FORMULATION AND EVALUATION OF TOLTERODINE TARTRATE SUSTAINED RELEASE CAPSULES

Dissertation

Submitted to

The Tamil Nadu Dr.M.G.R Medical University, Chennai

In partial fulfillment for the award of degree of

MASTER OF PHARMACY

in

PHARMACEUTICS

by

A.MOHAMED RIYAS

26113308

DEPARTMENT OF PHARMACEUTICS

ULTRA COLLEGE OF PHARMACY

4/235, COLLEGE ROAD, THASILDAR NAGAR

MADURAI-625020

OCTOBER-2013

DECLARATION

I hereby declare that this thesis work entitled **" FORMULATION AND EVALUATION OF TOLTERODINE TARTRATE SUSTAINED RELEASE CAPSULES"** Submitted to The Tamilnadu Dr.M.G.R Medical university, Chennai was carried out by me in the Department of Pharmaceutics, Ultra College of Pharmacy, Madurai under the valuable and efficient guidance of **Dr.C.Vijaya, M.PHARM., M.Pharm, Ph.D,** Professor & Head, Department of Pharmaceutics, Ultra college of Pharmacy, Madurai during the academic year Nov 2012- Oct 2013. I also declare that the matter embodied in it is a genuine work and the same has not formed the basis for the award of any degree, diploma, and associateship, fellowship of any other university or institution.

PLACE : MADURAI **(A.MOHAMED RIYAS)**

DATE :

ULTRA COLLEGE OF PHARMACY

4/235, COLLEGE ROAD

THASILDAR NAGAR

MADURAI.

CERTIFICATE

This is to certify that, the thesis work entitled **" FORMULATION AND EVALUATION OF TOLTERODINE TARTRATE SUSTAINED RELEASE CAPSULES"** submitted in partial fulfillment of the requirements for the award of degree of Master of Pharmacy in Pharmaceutics of The Tamil Nadu Dr.M.G.R Medical University, Chennai is a bonafide work carried out by **A.Mohamed Riyas** and was guided and supervised by me during the academic year Nov 2012- Oct 2013.

PLACE: MADURAI

DATE:

Dr.C.Vijaya, M.Pharm, Ph.D,

PROFESSOR & HEAD,

DEPARTMENT OF PHARMACEUTICS,

ULTRA COLLEGE OF PHARMACY,

MADURAI.

ULTRA COLLEGE OF PHARMACY

4/235, COLLEGE ROAD

THASILDAR NAGAR

MADURAI.

CERTIFICATE

This is to certify that, the thesis work entitled **" FORMULATION AND EVALUATION OF TOLTERODINE TARTRATE SUSTAINED RELEASE CAPSULES "** submitted in partial fulfillment of the requirements for the award of degree of Master of Pharmacy in Pharmaceutics of The Tamil Nadu Dr.M.G.R Medical University, Chennai is a bonafide work carried out by **A.Mohamed Riyas** and was guided and supervised by **Dr.C.Vijaya, M.Pharm, Ph.D,** Professor & Head, Department of Pharmaceutics, Ultra College of Pharmacy, Madurai during the academic year Nov 2012- Oct 2013

PLACE: MADURAI

DATE:

Dr.A.Babu Thandabani,

Principal,

Ultra College of Pharmacy,

Madurai-20

ULTRA COLLEGE OF PHARMACY

4/235, COLLEGE ROAD

THASILDAR NAGAR

MADURAI.

CERTIFICATE

This is to certify that, this thesis work entitled **" FORMULATION AND EVALUATION OF TOLTERODINE TARTRATE SUSTAINED RELEASE CAPSULES"** submitted in partial fulfillment of the requirements for the award of degree of Master of Pharmacy in Pharmaceutics of The Tamil Nadu Dr.M.G.R Medical University, Chennai is a bonafide work carried out by **A.Mohamed Riyas** and was guided and supervised by **Dr.C.Vijaya M.Pharm, Ph.D**, Professor & Head, Department of Pharmaceutics, Ultra College of Pharmacy, Madurai during the academic year Nov 2012- Oct 2013 was evaluated by us.

EXAMINERS:

1.

2

PLACE: MADURAI

DATE:

RA CHEM PHARMA LTD.

Regd. Off.: Plot No. 26 & 27, 1st Floor, Technocrat Industrial Estate, Balanagar, Hyderabad - 500 037. A.P., INDIA
Tel:+91-40-44758595, Fax:+91-40-44758596

Date: 23rd August 2013

CERTIFICATE

This is to certify that the thesis titled **"FORMULATION AND EVALUATION OF TOLTERODINE TARTRATE SUSTAINED RELEASE CAPSULES"** is submitted by **Mr. A. MOHAMED RIYAS,** Reg.No: 26113308 to the Department of Pharmaceutics, Ultra college of Pharmacy, The Tamilnadu Dr. MGR Medical University in partial fulfillment of the requirement for the degree of **M. Pharmacy (Pharmaceutics),** is a bonafied record work carried out by him under my supervision. The contents of this thesis, in full or in parts have not been submitted to any institute or university for the award of any degree or diploma.

External Supervisor

Dr. Thilek Kumar

(FDF Division)
Plot No. A-19/C, Road No. 18, IDA, Nacharam, Hyderabad - 500 076. A.P., India
Phone : +91-40-23443700 / 701 / 702, Fax : +91-40-23443703 Web : rachempharma.com

Dedicated to . . .

My Beloved Family, Teachers

&

Friends

-

ACKNOWLEDGEMENT

At the outsets I thank GOD for his Divine grace and strength in completing this thesis.

I am indebted to **Mr. Babu Thandapani**, **Principal, Ultra College of pharmacy**, **Madurai**, **The Tamil Nadu Dr. M.G.R Medical University,** for providing me necessary facilities to carry out the project work.

I am very glad to take this opportunity to express my sincere thanks and gratitude to my institutional guide **Dr.C.Vijaya, M.Pharm, Ph.D, Professor&Head, Ultra College of pharmacy, Madurai,** for his valuable guidance, constructive criticism and constant encouragement and also for making the requisite arrangements to enable me to complete my dissertation work.

I would like to thank **Mr. Senthil Kumar, Ultra College of pharmacy**, for his support and encouragement during my course.

I also thank to Non – teaching staff of Ultra College of pharmacy, who helped me directly or indirectly during my project work.

I am really indebted to **RA CHEM PHARMA Ltd**, Nacharam, Hyderabad, for providing me a platform to develop my skills and expertise in the subject and for extending association to my study.

With great pleasure I acknowledge my sincere thanks and gratitude to my industrial guide **Dr. M. Thilek Kumar**, **FR&D,** at **RA CHEM PHARMA Ltd**. (Research labs), Hyderabad. For providing me the necessary laboratory facilities to carry out this work with great ease and precision.

I am indebted to **Mr. Sirish kumar, Executive Director, RA CHEM PHARMA Ltd,** for allowing me to accomplish the project work in this industry.

I am very thankful to **Dr. J. Balasubramaniam, GM, Research and Development, RA CHEM PHARMA Ltd,** for the necessary guidance and support and constant encouragement, help and co-operation during my project work.

I also thankful to the scientists **Mr. Niranjan, Mr. Y. Rajesh, Mr. Ravi, Mr. Hema kumar, Mr. Praveen, Mr. Satyanarayana, Mr. Sreekanth, Mr. Aditya, Mr. Raja Rao, Mr. Krishna Mohan, Mr. Pradeep, Mr. Harendra Pradap, Ms. Swathi, Ms.Vishnu priya** for their company, constant encouragement, help and co-operation during my project work.

I also thank to all other friends from Rachem Pharma Ltd for their support during the course.

I thank to my friends Mr. T. Chozharajan, Mr. D. Prawin, for their fabulous support and who have willingly helped me out with their abilities.

I specially thank to Lab instructor Mrs, Masila, Department of Pharmaceutics, Ultra College of Pharmacy, Madurai.

Words are not enough to express endless thanks to all my friends for their help and unconditional support during my project work.

I would like to thank my brother **A. Mohamed Mustafa** and my sister **A.Shafana Begam** for their co-operation, support and encouragement.

I owe my deepest regards to my **parents** for caring me with their emphatic encouragement and preserving support all through the way. I cannot express in words about what their appreciation and moral means for me. They have been like foundation upon which the building of my life rests.

A.MOHAMED RIYAS

1. INTRODUCTION

1.1 DRUG DELIVERY SYSTEM

The treatment of acute diseases or chronic illness has been achieved by delivery of drugs to the patients for many years. These drug delivery systems include tablets, injectables, suspensions, creams, ointments, liquids and aerosols. Today these conventional drug delivery systems are widely used. The term **drug delivery** can be defined as techniques that are used to get the therapeutic agents inside the human body. Another role of the delivery systems is to allow the safe application of the drug. This includes that the drug in the formulation must be chemically, physically and microbiologically stable. Side-effects of the drug and drug interactions should be avoided or minimised by the use of suitable drug delivery systems. The delivery systems also need to improve the patient's compliance with the pharmacotherapy by the development of convenient applications. For example, one can improve patient compliance by developing an oral dosage form where previously only parenteral application was possible. Finally, the delivery system needs to be reliable and its formulation needs to be technically feasible. This means the Pharmaceutical quality of the delivery systems needs to be assured, drug release from the system needs to be reproducible and the influence of the body on drug release should be minimized. (For example, food effects after oral administration.) [1, 2]

Drug delivery systems

1. Conventional drug delivery systems

2. Controlled drug delivery systems

1.2 Conventional Drug Delivery Systems

Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional drug delivery is effective, but some drugs which possess narrow therapeutic window and which cause irritation to gastric mucosa requires modified drug delivery system to achieve desired therapeutic effect. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity and improved patient convenience. The main goal of modified drug delivery systems is to improve the effectiveness of drug therapies.

Conventional dosage forms are rapidly absorbed, with the ascending and descending portions of the concentrations versus time curve reflecting primarily the rate of absorption and elimination, respectively. Because of the rapid rate of absorption from conventional dosage forms, drugs are usually administered more than once daily, with the frequency being dependent on biological half- life (t½) and duration of pharmacological effect. The time of dosing may also be effected by therapeutic index of a drug. [3, 4, 5]

1.2.1 Disadvantages of Conventional Drug Delivery Systems

- In conventional oral drug delivery systems, there is little or no control over the release of the drug and effective concentration at the target site.
- The dosing pattern in conventional dosage forms results in constantly changing, unpredictable and often sub-therapeutic plasma concentrations, leading to marked side effects in some cases.

- Conventional drug delivery system is not suitable for the drugs which cause irritation to the gastric mucosa.
- The rate and extent of absorption of drug from conventional formulations may vary greatly, depending on the factors such as physicochemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the gastrointestinal tract, gastrointestinal motility and so on.[6]

1.3 MODIFIED DRUG DELIVERY SYSTEMS

Dosage forms can be designed to modify the release of the drug over a given time or after the dosage form reaches the required location. Drug release only occurs sometime after the administration or for a prolonged period of time or to a specific targeted site in the body. Modifications in drug release are often desirable to increase the stability, safety and efficacy of the drug, to improve the therapeutic outcome of the drug treatment and/or to increase patient compliance and convenience of administration.[7]

Classification:

Modified Release dosage form may be classified as

- **Extended Release**
  - Sustained Release
  - Controlled Release
- **Delayed Release**

1.3.1. Extended Release:

This type of oral DDS allows the drug to be released over prolonged time periods. By extending the release profile of a drug, the frequency of dosing can be reduced. Extended release can be achieved using sustained or controlled-release dosage forms.

1.3.2. Sustained Release:

This term is constantly used to describe a pharmaceutical dosage form formulated to retard the release of the therapeutic agent such that its appearance in the systemic circulation is delayed and prolonged and its plasma profile is sustained in duration. The onset of its pharmacological action is often delayed, and the duration of its therapeutic effect is sustained.

In orally administered dosage forms, this duration is in hours and critically depends on the residence time of the dosage form in GI tract, whereas in the case of injectable this period may vary from days to months.

1.3.2a. Advantages of SR Dosage Forms:

- ✓ Improved patient compliance due to reduced frequency of drug administration.
- ✓ The blood level oscillations characteristic of conventional dosage forms is reduced.
- ✓ A less obvious advantage that the total amount of drug administered can be reduced, thus maximizing availability with minimum dose.
- ✓ Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of high availability drug can be reduced by formulation in an extended action form.
- ✓ The safety margin of high potency drugs can be increased, and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.
- ✓ Reliable therapy. [9]

1.3.2b. Disadvantages:

- Administration of SR medication does not permit the prompt termination of therapy.
- Less flexibility in adjusting dosage regimen.
- Sustained release forms are designed for normal population, i.e., on the basis of biological half-lives. Consequently, disease states that alter drug disposition, significant patient variation, and so forth are not accommodated.
- Economic factors. [9]

1.3.2c. Drug candidates those are suitable for SR Dosage Forms:

- ✓ Should be effectively absorbed in small intestine.
- ✓ Biological half- life should lie within 1-12hours.
- ✓ Dosage that is not titrated according to individual.
- ✓ Small doses(<1g) [9]

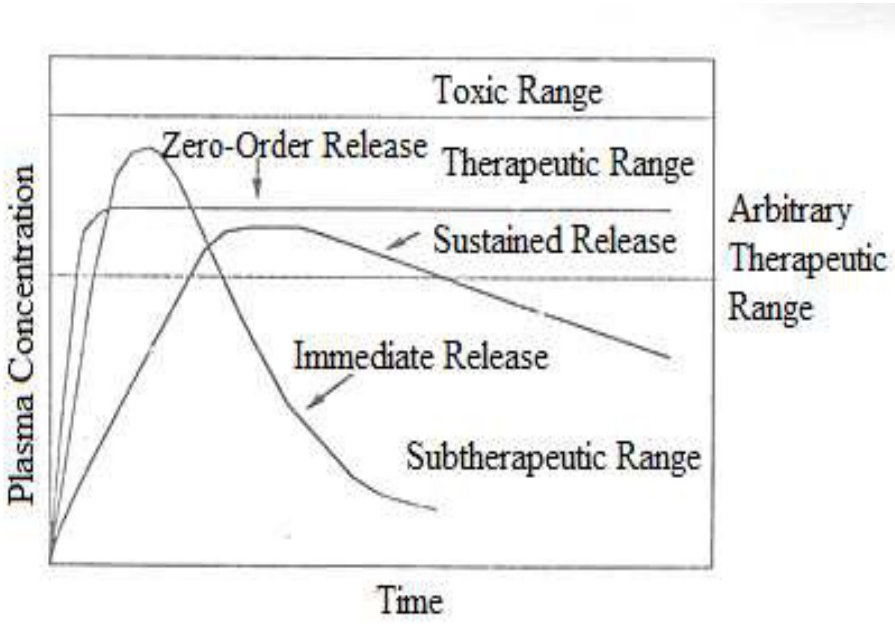


Fig.1 Plasma Dug Concentration Profiles for Conventional Tablet Formulation, a Sustained Release Formulation and a Zero Order Controlled Release Formulation.

SR system generally don't attain zero order type release and usually try to mimic zero order release by providing drug in a slow first order. Repeat action tablet are an alternative method of sustained release in which multiple doses of drug are contained within a dosage form and each dose is released at a periodic interval. Delayed release system, in contrast, may not be sustaining, since often the function of these dosage forms is to maintain the drug in the dosage for some time before its release, Eg: Enteric coated tablet.

The ideal way of providing an exact amount of drug at the site of action for a precise time period is usually approximated by most systems. This approximation is achieved by creating a constant

concentration in the body organ over an extended time; in other words, the amount of drug entering the system is equivalent to the amount of drug removed from the system. All forms of metabolism and excretion are included in the removal process: urinary excretion, enterohepatic recycling, sweat, fecal and so on. Since, for most of the drugs these elimination processes are firstorder, it can be said that a certain blood level, the drug will have a specific rate of elimination. The idea is to deliver drug at this exact rate for an extended period. This is represented mathematically as following,

$$\text{Rate in} = \text{Rate out} = k_{\text{elim}} \times C_d \times V_d$$

Where C_d is the desired drug level,

V_d is the volume of distribution, and

k_{elim} is the rate constant of drug elimination from the body.

1.3.3. PHYSICOCHEMICAL FACTORS INFLUENCING ORAL SUSTAINED-RELEASE DOSAGE FORM DESIGN [13, 14]

a. Dose size

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5- 1.0g is considered maximal for a conventional dosage form. This also holds for sustained release dosage form. Compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety involved in administration of large amount of a drug with a narrow therapeutic range.

b. Ionization, *pka* and aqueous solubility

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the *pka* of the compound and the absorptive environment. Presenting the drug in an unchanged form is advantageous for drug permeation. Unfortunately, the situation is made more complex by the fact that the drug's aqueous solubility will generally be decreased by conversion to unchanged form. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of pH on the release process must be defined.

Compounds with very low solubility (<0.01mg/ml) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. So it is obvious that the solubility of the compound will be poor choices for slightly soluble drugs, since the driving force for diffusion, which is the drug's concentration in solution, will be low.

c. Partition Coefficient

When a drug is administered to the GI tract, it must cross a variety of biological

Membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipidic; therefore the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer time. In case of compounds with very low partition coefficient, it is very difficult for them to penetrate the membrane, resulting in poor

bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on the partitioning characteristics of the drug.

d. Stability

Orally administered drugs can be subjected to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state. For the dosage form that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial; this is also true for systems that delay release until the dosage form reaches the small intestine. Compounds that are unstable in small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs are delivered in the small intestine and, hence, is subject to degradation.

1.3.4. BIOLOGICAL FACTORS INFLUENCING ORAL SUSTAINED-RELEASE DOSAGE FORM DESIGN [13,14]

· Biological half- life.

· Absorption.

· Metabolism.

a. Biological half life

The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life ($t_{1/2}$). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that

permanently remove drug from the blood stream. Therapeutic compounds with short half-life are generally are excellent candidate for SR formulation, as this can reduce dosing frequency. In general, drugs with half-life's shorter than 2 hours such as furosemide or levodopa are poor candidates for SR preparation. Compounds with long half-lives, more than 8 hours are also generally not used in sustaining form, since their effect is already sustained. Digoxin and phenytoin are the examples.

b. Absorption

Since the purpose of forming a SR product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours; otherwise, the device will pass out of the potential absorptive regions before drug release is complete. This corresponds to a minimum apparent absorption rate constant of 0.17-0.23h-1 to give 80-95% over this time period. Hence, it assumes that the absorption of the drug should occur at a relatively uniform rate over the entire length of small intestine. For many compounds this is not true. If a drug is absorbed by active transport or transport is limited to a specific region of intestine, SR preparation may be disadvantageous to absorption. One method to provide sustaining mechanisms of delivery for compounds is to maintain them within the stomach. This allows slow release of the drug, which then travels to the absorptive site. These methods have been developed as a consequence of the observation that co-administration results in sustaining effect. One such attempt is to formulate low density pellet or capsule. Another approach is that of bio adhesive materials.

c. Metabolism

Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage form. Hence criteria for the drug to be used for formulating Sustained-Release dosage form is,

· Drug should have low half-life(<5 hrs)

· Drug should be freely soluble in water.

· Drug should have larger therapeutic window.

· Drug should be absorbed throughout the GIT.

Even a drug that is poorly water soluble can be formulated in SR dosage form. For the same, the solubility of the drug should be increased by the suitable system and later on that is formulated in the SR dosage form. But during this the crystallization of the drug, that is taking place as the drug is entering in the systemic circulation, should be prevented.

1.3.5. Controlled Release Dosage:

CR dosage form is generally accomplished by attempting to obtain "zero- order" release from the dosage form which is independent of the amount of drug in the delivery system (i.e., a constant release rate). Sustained Release systems generally do not attain this type of release and usually try to mimic zero order release by providing drug in a slow first order fashion (i.e., concentration dependent).

The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug.

Depending upon the manner of drug release, these systems are classified as follows:

a. Continuous release systems

These systems release the drug for a prolonged period of time along the entire length of gastrointestinal tract with normal transit of the dosage form.

The various systems under this category are as follows:

A. Dissolution controlled release systems

B. Diffusion controlled release systems

C. Dissolution and diffusion controlled release systems

D. Ion exchange resin- drug complexes

E. pH dependent formulation

F. Osmotic pressure controlled systems [13]

b. Delayed transit and continuous release systems

These systems are designed to prolong their residence in the GI tract along with their release. Often the dosage form is fabricated to retain in the stomach and hence the drug present therein should be stable in gastric pH. Systems included in this category are mucoadhesive systems and size based systems. [13]

1.3.6. Delayed Release

A Delayed Release dosage form is designed to release the drug at a time other than promptly after administration. Dosage forms can be designed to modify the release of the drug over a given time or after the dosage form reaches the required location.

Delayed Release oral dosage forms can control where the drug is to be released, e.g. when the dosage form reaches the small intestine (enteric-coated dosage forms) or the colon (colon-specific dosage forms).

Delayed Release systems release a bolus of the drug after a predetermined time in a predetermined location, i.e. they do not release the drug immediately after ingestion, for example enteric-coated tablets, pulsatile-release capsules.

Delayed Release dosage forms are designed to provide spatial placement or temporal targeted delivery of a drug to the distal human gut. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to desired rate of drug release to target tissue over a specified period of time.

The correct selection and balance of excipients and processes in solid dosage formulations are designed either for improving the micromeritic or macromeritic properties of materials during manufacture and/or for providing a desired drug delivery system. The most commonly used pharmaceutical sustained release solid oral dosage forms today include tablets, capsules, granules and pellets. [14, 15]

1.4 MULTIPARTICULATES / MULTI UNIT DOSAGE FORMS

Multiple unit dosage forms are essential where drug-excipients or drug-drug physicochemical interaction is possible in a single-unit formulation, they are also known to have less variance in transit time through the gastro intestinal tract than single unit dosage forms. They are usually delivered in hard gelatin capsules or made into tablets that disintegrate instantly.

Types of Multiple unit dosage forms comprise

- Pellets
- Granules

- Mini tablets mini depots
- Micro particles (Microspheres or Microcapsules) and Nano particles

Multi particulates are

- Filled into hard-gelatin capsules
- Compressed tablets
- Suspended in liquids or
- Packed in sachets.

1.4.1 Features of the Performance of Multiparticulates

Multi particulate dosage forms have a number of useful features which can be used for the advantage in modified release forms. Foremost is their ability to overcome the variation in performance which may arise through variation in gastrointestinal transit time and, in particular, variation occasioned by erratic gastric emptying. The size of most multi particulates enables them to pass through the constricted pyrolic sphincter so they are able to distribute themselves along the entire gastrointestinal tract. As the dose of drug is spread out over a large number of particles, then the consequences of failure of a few units has nothing like the potential consequences of failure through dose dumping of a single coated tablet used as a modified release dosage form. Additionally, as the drug is not all concentrated in one single unit, considerations of an irritant effect to the mucosal lining of the gastrointestinal tract are very much reduced. [16]

1.5 PELLETS[11,19]

Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free flowing spherical or semi spherical solid units typically from about 0.5-1.5mm. These are intended usually for oral administration.

1.**5.1 Desirable Properties of Pellets:**

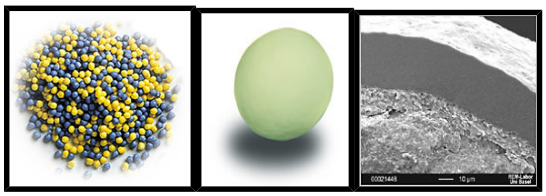
Pellets may be uncoated type or coated type.

a) Uncoated pellets:

Uncoated pellets must have following properties

- Uniform spherical shape and smooth surface.
- Optimum size of pellets is between 600 and 1000?m.
- Good flow properties.
- High physical strength and integrity.
- Good hardness and low friability.
- High bulk density.
- Ease and superior properties for coating.
- Reproducible packing of beds and columns.

b) Coated pellets: Along with the above properties, the coated pellets must contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits.



(a) Pellets, (b) Perfect pellet, (c) Coated pellet

Figure 2: Different types of pellets

1.5.2 Stages in Pellet Formation and Growth:

Formation and growth of pellets can be divided into four stages:

1. Pendular state
2. Funicular state
3. Capillary state
4. Droplet state.

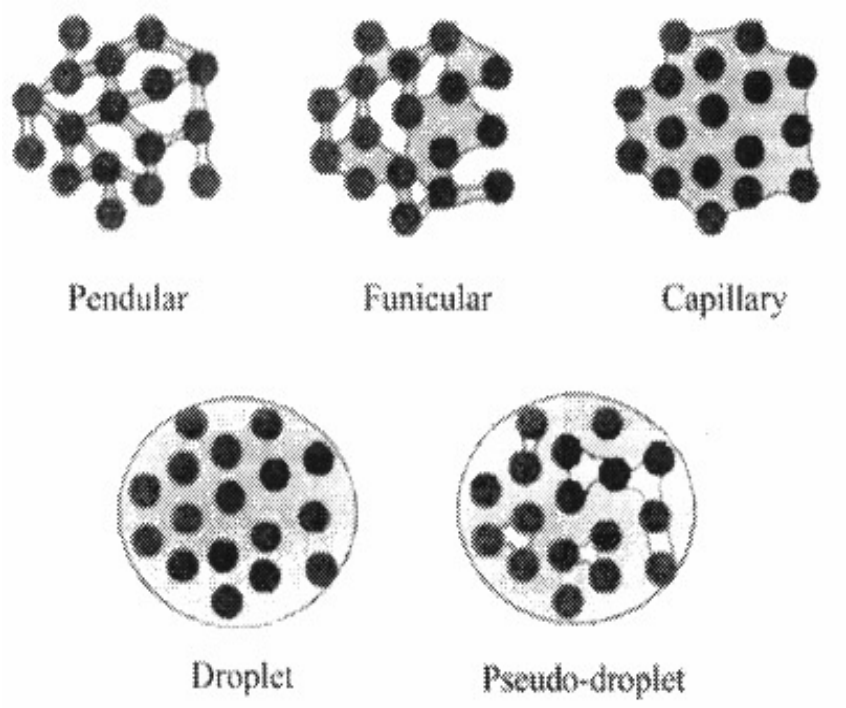


Figure 3: Different formal spatial structures of liquid-bound agglomerates

1.5.3 Advantages of pellets:

- Improved appearance of the product which is having fine pharmaceutically elegant.
- Pelletization offers flexibility in dosage form design and development.
- Pellets improve the flow properties in formulation development.
- Pellets are less susceptible to dose dumping.
- It reduces localized concentration of irritative drugs.

- It improves safety and efficacy of a drug.
- Pellets offer reduced variation in gastric emptying rate and transit time.
- Pellets disperse freely in G.I.T. and invariably maximize drug absorption and also reduce peak plasma fluctuation.
- Pellets ensure improved flow properties in formulation development.
- Pelletization is a convenient way to manage the separation of incompatible drugs.
- Chemically incompatible products can be formed into pellets & delivered in a single dose by encapsulating them.
- The most important reason for the wide acceptance of multiple unit products is the rapid increase in popularity of oral pellets dosage forms, Pellets oral solid dosage forms are usually intended either for delivery of the drug at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of time.[11]

1.5.4 Disadvantages of pellets:

- The manufacturing of multiple unit dosage forms is more complicated and more expensive.
- The filling into gelatin capsules is difficult to accomplish, especially in the case where different subunits are involved.
- Scale-up of pellets is a very complicated one.

1.5.5 Theory of pellet formation and growth

Before selection and optimization of any pelletization/granulation process, it is important to understand the fundamental mechanisms of pellet formation and growth. Different theories have been postulated related to the mechanism of formation and growth of pellets. Some of these theories are derived from experimental results while others are derived by visual observations. Out of these hypothetical theories the most convincing classification of Pelletization process, involves three consecutive regions: nucleation, transition and ball growth. However, based on the

experiments on the mechanism of pellet formation and growth, the following steps were proposed: nucleation, coalescence, layering and abrasion transfer.

Nucleation is a stage of pelletization process that occurs whenever a powder is wetted with solvent system. The primitive particles are drawn together to form three-phase air-water-liquid nuclei system which are held together by liquid bridges that are pendular in nature. The reduction of particle size will improve the bonding strength between them. Further the size, the rate and the extent of nuclear formation depends upon the size of the particles, the moisture content, the viscosity of the binding particles, the wet ability of the substrate and the processing conditions, such as tumbling and drying rates.

Nucleation is followed by a transition phase where the growth mechanisms affecting are coalescence and layering. Coalescence is defined as the formation of large-sized particles by random collision of well-formed nuclei, this mechanism require slightly excess moisture on the surface of the nuclei although the number of nuclei is progressively reduced even though the total mass of the system remains unchanged during this operation. Layering is a slow growth mechanism and with the successive addition of fragments and fines on an already formed nuclei. In the layering step, the number of particles remains constant while the total mass of the system increases due to increasing particle size as a function of time. The fragments or fine particles can be formed by particle size reduction.

The fines and the fragments produced through size reduction are taken up by larger pellets. Production of fines and subsequent coalescence and layering continues until the number of collisions declines rapidly, thereby leading to a reduction in the rate of growth of the pellets. At this point the third phase, the ball growth region, is reached. The main mechanism in the ball

growth phase is the abrasion transfer which involves the transfer of materials from one granule formed to another without any preference in either direction. This phase does not result in any change in the total number or mass of the particles. However, the particles undergo a continuous change in their size as long as the conditions that lead to the transfer of material exist. [11, 12]

1.5.6 Pelletization techniques [11,19]

Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free-flowing, spherical or semi-spherical units, referred to as pellets.

The most commonly used and intensely investigated pelletization processes are [12]

1. Powder layering,
2. Solution/Suspension layering, and
3. Extrusion–Spheronization.

Compaction and drug layering are the most widely used pelletization techniques in Pharmaceutical industry. Other pelletization methods such a globulation, balling and compression are also used in development of pharmaceutical pellets although in a limited scale

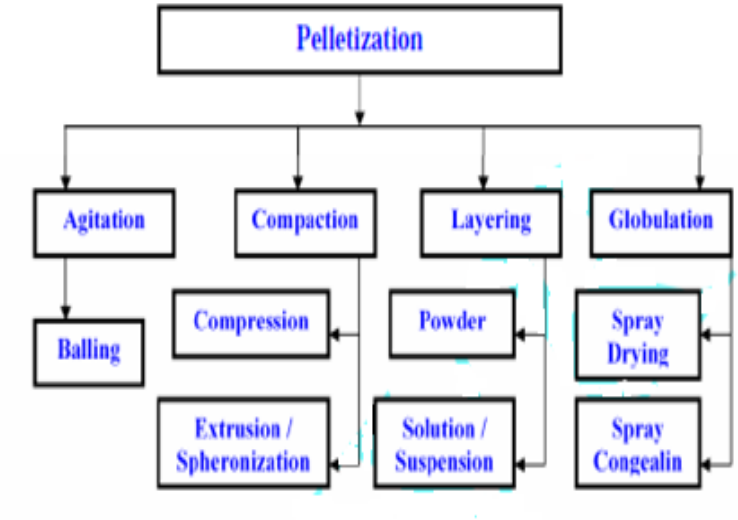


Fig.No 4: Different pelletization techniques

1.5.6.1 LAYERING

a) Powder layering:

Powder layering involves the deposition of successive layers of dry powders of drugs and excipients of formulation on spheres of inert material of sugar with the help of a binding liquid during powder layering a binding solution and a finely milled powder are added simultaneously to a bed of starter spheres at a controlled rate. In the initial stages the drug particles are bound to the starter spheres and subsequently to the forming pellets with the help of liquid bridges originated from the sprayed binding liquid. Successive layering of the drug and binding solution continues until the desired pellet size is achieved. [10, 12]

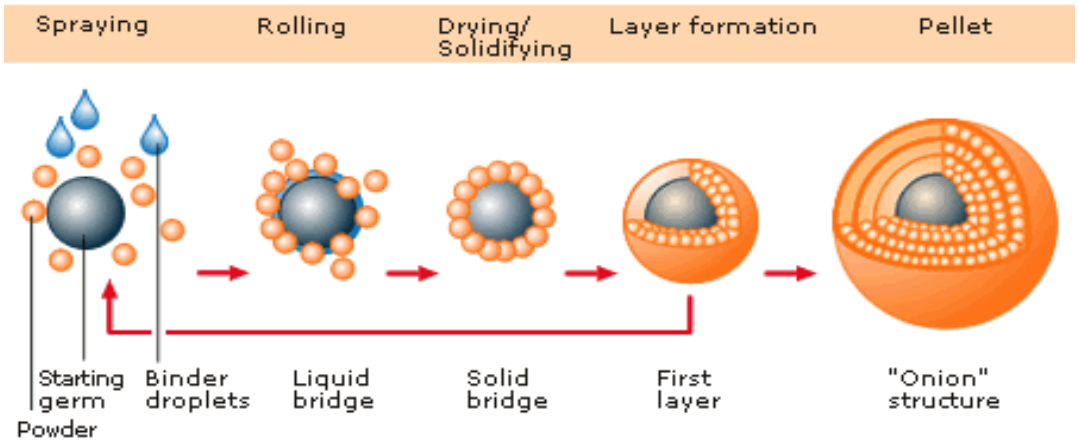


Fig.No.5: Depicts the principle of powder layering

b) Solution / Suspension layering:

Solution/suspension layering involves the deposition of successive layers of solutions or suspensions of drug substances and binders over the starter/non-pareil seeds, which is an inert material or crystals/granules of the same drug. During solution or suspension layering all the components of the formulation are dissolved or dispersed in the application medium. As the solution or suspension is sprayed on to the spheres (staring core) the droplets impinge on the starter spheres and spread evenly on the surface provided favorable drying and fluid conditions. This is followed by a drying phase which allows dissolved material to crystallize and form solid bridges between the core and initial layer of the drug substance as well as among the successive layers of the drug substances. The process continues until the desired pellet size is achieved.

In fact the coating process involved in general is applicable to solution or suspension layering technology. Consequently conventional coating pans, fluidized beds, centrifugal granulators, Wurster coaters have been used successively used to manufacture pellets by this

method. The efficiency of the process and the quality of the pellets produced are in part related to the type of equipment used. [10, 12]

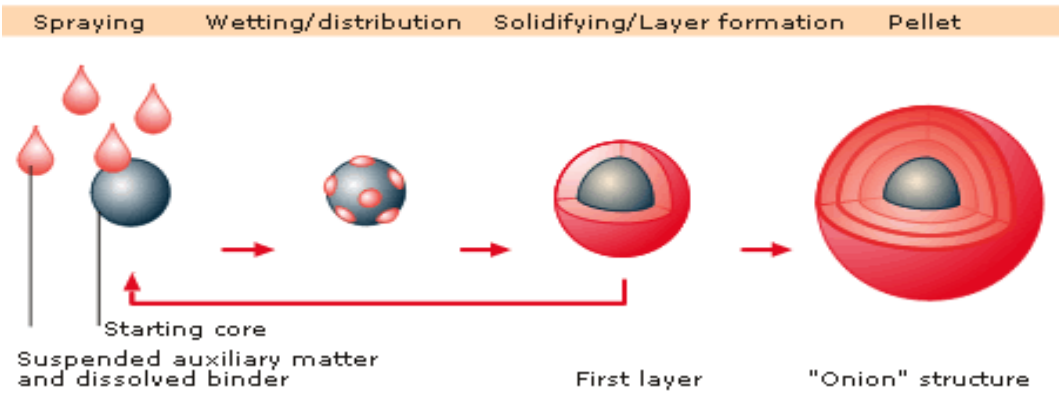


Fig.No.6: Depicts the principle of solution and suspension layering,

c) Direct pelletization:

Direct pelletization process leads to formation of homogeneous pellets which have microscopically uniform structure and no core can be detected. The pelletization of powdered starting materials is facilitated by the addition of binder liquid and a suitable movement of wetted powders. The impact and acceleration forces that occur in this process result in the formation of agglomerates, which become rounded out into uniform and dense pellets. The speed of rotation has a direct influence on the density and size of the pellets. The solidification of the pellets is achieved by drying the liquid. Direct pelletization processes are mainly performed in high shear mixers and fluidized bed equipment. [11]

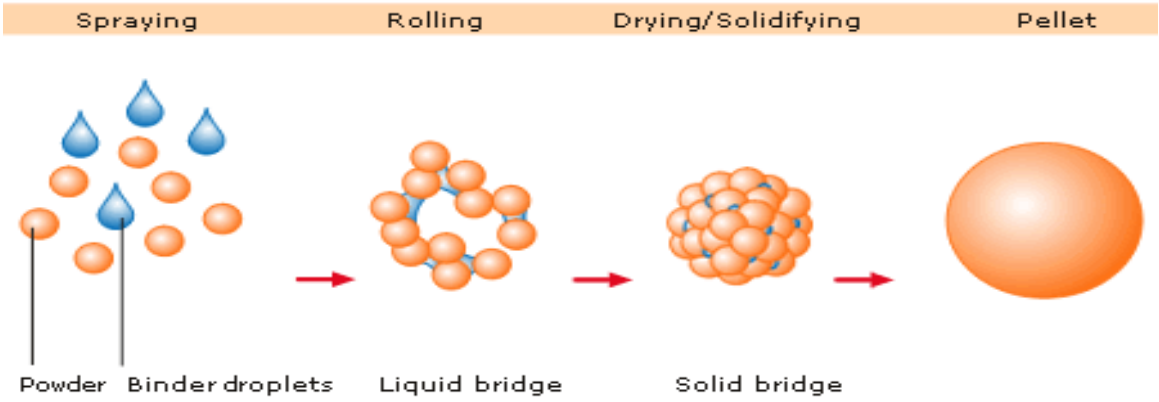


Fig No.7: Depicts the principle of direct pelletization,

1.5.6.2 COMPREESION

a) Pelletization by Extrusion and spheronization:

Extrusion–Spheronization is a multistep process involving dry mixing, wet granulation, extrusion, spheronization, drying, and screening. The first step is dry mixing of the drug and excipients in suitable mixers followed by wet granulation, in which the powder is converted into a plastic mass that can be easily extruded. The extruded strands are transferred into a spheronizer, where they are instantaneously broken into short cylindrical rods on contact with the rotating friction plate and are pushed outward and up the stationary wall of the processing chamber by centrifugal force. Finally, owing to gravity, the particles fall back to the friction plate, and the cycle is repeated until the desired sphericity is achieved. [15, 16]

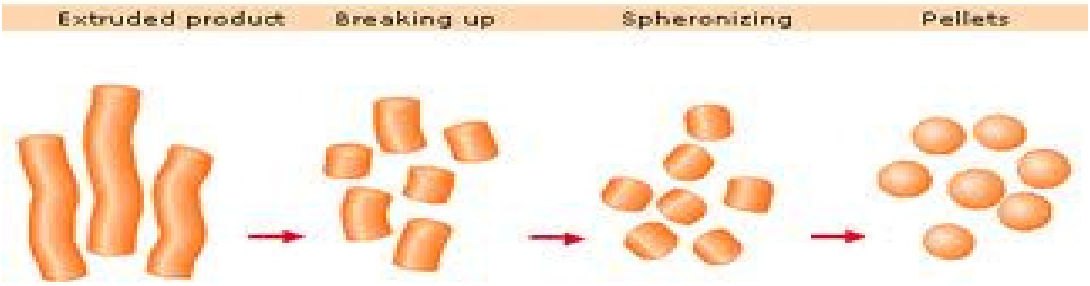


Fig No.8: Depicts the principle of Extrusion & Spheronization,

b) Compression:

It is one type of compaction technique for preparing pellets. Compacting mixtures or blends of active ingredients and excipients under pressure prepare pellets of definite sizes and shapes. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablets manufacturing.

1.5.6.3 AGITATION

a)Balling:

It is the pelletization process in which pellets are formed by a continuous rolling and tumbling motion in pans, discs, drums or mixtures. The process consists of conversion of finely divided particles in to spherical particles upon the addition of appropriate amounts of liquid. The liquid may be added prior or during the agitation stage. As powder come in contact with a liquid phase, they form agglomerates or nuclei which are initially bound together by liquid bridges that are subsequently replaced by solid bridges derived from the hardening binder or any other dissolved material within the liquid phase.

1.5.6.4 GLOBULATION or droplet formation consists two related processes, spray drying and spray congealing, involve atomization. Atomization of hot melts solution or suspensions to generate spherical particles pellets.

a) Spray drying:

During spray drying, drug entities in solution or suspension are sprayed, into a hot air stream to generate dry and highly spherical particles. As the atomized droplets come on contact with hot air, evaporation of the application medium initiated. The drying process continues until the entire application medium is driven off and solid particles are formed. Generally, spray dried pellets tend to be porous. This process is commonly used for improving the dissolution rates; hence bioavailability of poorly soluble drugs.

b) Spray congealing:

It is the process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes or fatty acids, and is sprayed into an air chamber where the temperature is kept below the melting point of the formulation components, to provide appropriate processing conditions for spherical congealing of pellets. A critical requirement in a spray congealing process is that the formulation components have sharp melting points or narrow melting zones. Pellets produced by this process are dense and nonporous. Both immediate and controlled release pellets can be prepared in this process depending on the physiochemical properties of the ingredients and other formulation variables.

1.5.6.5 OTHER PELLETIZATION METHODS [19]

a) Cryopelletization:

In cryopelletization, droplets of liquid formulation are recovered in to solid spherical particles or pellets by employing liquid nitrogen as the fixing medium. This technology can produce drug-loaded pellets by allowing droplets of solution or suspension to come in contact with liquid nitrogen at -160^{0}C. The procedure permits instant and even freezing of the material being processed due to the repaid heat transfer which occurs between the droplets and the liquid nitrogen. The pellets are dried in conventional freeze dryers.

The most critical step in **Cryopelletization** is droplet formation, which is influenced not only by formulation variables such as viscosity, surface tension and solid contents, but also by equipment design and the corresponding processing variables. The diameter and design of the shearing edges of the holes on the container plates are also critical. For instance, the diameter of the holes determines the flow rate, which in turn is governed by the viscosity of the formulation. The diameter of holes also influences the size and shape of the pellets. The smaller the nozzle diameter, the smaller the pellets produced. The shape of droplets depends on the distance of the droplets travel before contacting the liquid nitrogen. [11, 19]

1.6 PELLET COATING PROCESS

The coating process for pellets is carried out primarily in order to modify the release of the drug from the pelletized drug delivery systems. Following are the some of the Coating equipments used for this purpose

1. Conventional Coating Pan

2. Perforated Coating Pan

3. Fluidized Bed Processor

1.6.1 Conventional Coating Pan:

The standard coating pan system consists of a circular metal pan mounted somewhat angularly on a stand, the pan is rotated on its horizontal axis by a motor, the hot air is directed into the pan and onto the bed surface, and is exhausted by means of ducts positioned through the front of the pan. Coating solutions are applied by spraying the material on the bed surface. In this technique the granules or sugar spheres are placed in the coating pan and the coating solution is sprayed on the granules by atomizer with pressure.

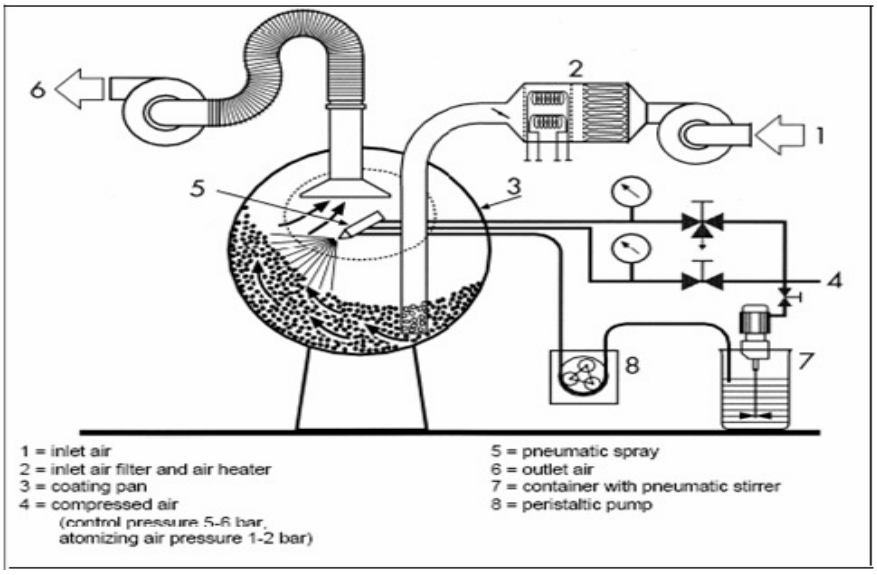


Fig No.9: Conventional Coating Pan

1.6.2 The perforated Coating Pan:

Perforated pan coaters are efficient drying systems with high coating capacity, and can be completely automated for both sugar coating and film coating processes. There are four different type of coaters available Acela-Cota, Hi-Coater, Driacoater, Glatt coater. In all four of these perforated pan systems the coating solution is applied to the surface of the rotating bed of pellets through spraying nozzles that are positioned inside the drum.[10]

1.6.3 Fluidized Bed Processor:

- One machine can perform multiple functions like coating, drying, granulation and pelleting.
- Highly efficient drying system.
- Aqueous or organic coatings can be applied.
- Uniform continuous product coating achieved.

Applications:

1. Ideal for a wide range of process applications include coating hearing drying agglomeration and granulation.
2. Ideal for control release film coating, pellet granulation and hot melt coating.
3. Suitable for coating of micro particles, granules, pellets or tablets.
4. Specific manipulation of the particle surface characteristics. Protection of the product against moisture, light, air.

Principle of operation:

With fluid bed coating particles are fluidized and the coating fluid sprayed on and dried. Small droplets and a low viscosity of the spray medium ensure an even product coating.

Different types of fluidized bed processors are

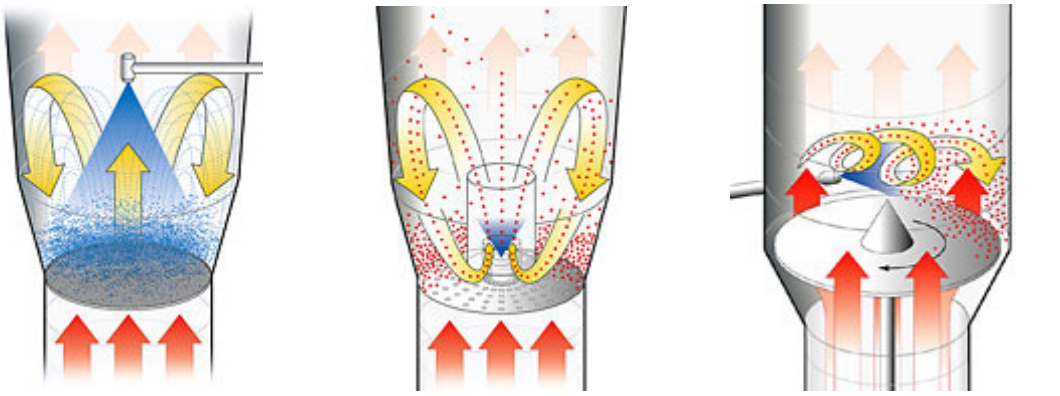
A) Top spray coating

B) Bottom spray coating (Wurster coating)

C) Tangential spray coating (Rotor pellet coating)

1.6.3.1 Top spray coating:

This process is used to spray binder solution for powder granulation. Particles are fluidized in the flow of heated air, which is introduced into the product container via a base plate. The binder solution is sprayed into the fluid bed from above against the air flow (counter current) by using nozzle. Air volume is adjusted to have the center of the particle stream very close to the nozzle. Drying takes place as the particles to move upwards in the air flow.



TOP SPRAY **BOTTOM SPRAY** **TANGENTIAL SPRAY**

Fig No.10: Depicts the types of fluid bed processor

Applications:

- Preferred when a taste masking coating is applied. Additionally suitable for the application of hot melt coating.
- Continuous spray coater is particularly suitable for protective coatings/colour coating.

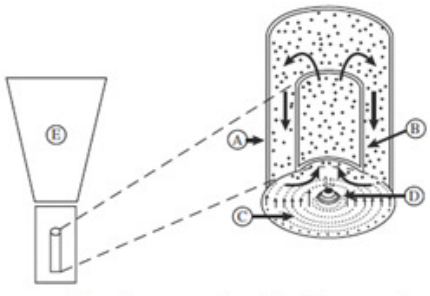
1.6.3.2 Bottom Spray coating (Wurster coating):

The process is suitable for pellet suspension coating or film/sugar coating, particularly useful for a control release active ingredients.

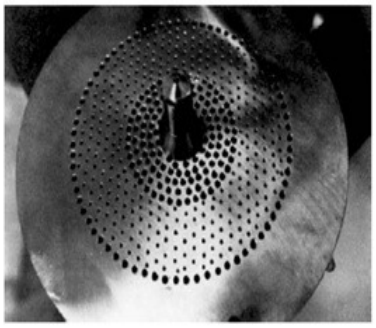
In this process, a complete sealing of the surface can be achieved with a low usage of coating substance. When the hot air flows through the bottom screen of container and coating column, it will generate the siphonage principle. Convection is created through the strong force from bottom toward top. The granules will then fall down and will be sucked into the coating column again, while the bottom spray gun will spray towards top to achieve coating purpose. As the particles continue travelling upwards, they dry and fall outside the Wurster tube back towards the base plate.

Table No.1: Parameters Used in Bottom Spray Equipment

Inlet temperature	38-42ºC
Product temperature	32-36ºC
Exhaust temperature	32-38ºC
Spray rate	8-12mg/min
Peristaltic pump	12-18 rpm



Schematic representation of the Wurster product chamber and process. (A) product chamber, (B) partition, (C) orifice plate, (D) nozzle, and (E) expansion chamber.



Air distributer or orifice plate of a Wurster coater.

Fig No.11: Orifice plate of a Wurster coater

Applications:

- Preferred for the application of modified release coatings to a wide variety of multi particulates.
- And also suitable for drug layering when the drug does is in the low to medium range.

1.6.3.3 Tangential spray coating (Rotor pellet coating):

This process is particularly suitable for pellet powder coating, suspension coating or film/sugar coating.

In this process the cores are placed on the turntables and hot air is blown upward between the turntables and the granulation area. The passage of air causes the cores to roll on the turntables. At the same time, the coating solution is sprayed on the rolling cores through the pump and spray gun. The process involves simultaneous coating and drying of the cores, layer after layer, until the repeated actions achieve the desired coating thickness or granule size.

Applications:

- Suitable for the application of modified release film coatings to a wide range of multi particulate products.
- Ideal for drug layering when the dose is medium to high.
- Also useful as a spheronizing process for producing spheres from powders.

1.7 EXCIPIENTS FOR PELLETS

Formulation aids or excipients are added to pharmaceutical dosage forms mainly to produce satisfactory delivery of the drug to the intended site, to impart favorable characteristics to the dosage form and to facilitate the manufacture of the product.

Pellets are to be intended to be administered orally; the excipients used in the pellet dosage forms are typically the same as those used in tablets or capsules formulations. Excipients are disintegrant, surfactants, pH adjusters, separating agents, spheronization enhancers, glidants and release modifiers etc. Some examples of such excipients are given. [17,18]

Table No.2: Commonly Used Excipients for pellets

Filler	MCC, starch, sucrose, lactose, mannitol
Binder	Gelatin, HPC, HPMC, MC, PVP, sucrose, starch
Lubricant	Calcium stearate, glycerine, PEG, Mg. stearate
Separating agent	Kaolin, talc, silicon dioxide
Disintegrant	Alginates, croscarmellose sodium
pH adjuster	Citrate, phosphate, meglumine.
Surfactant	Polysorbate, SLS
Spheronization enhancer	MCC , sodium CMC
Glidant	Talc, starch, Mg stearate.
Release modifier	Ethyl cellulose, carnauba wax, shellac.

1.8 CAPSULES

Capsules are gelatin shells filled with the ingredients that make up an individual dose. Dry powders, semi-solids, and liquids that do not dissolve gelatin may be encapsulated. Capsules account for about 20% of all prescriptions dispensed.

Capsules are available in many different sizes and shapes and can be used for administration of powders, semisolids and liquids.

1.8.1 Capsules Standards and limits

Description:

It should comply with specifications of product.

Content of active ingredients:

90 to110% of label claim or as per In house limit.

Uniformity of weight:

Table No.3: Content uniformity limits

Average weight of capsules content	**Percentage deviations allowed**
less than 300mg	10%
300mg or more	7.5%

1.9 DISEASE PROFILE[20, 21, 28]

1.9.1 OVERACTIVE BLADDER:

Overactive bladder (OAB) is a condition that results from sudden, involuntary contraction of the muscle in the wall of the urinary bladder. It is commonly characterized by urinary urgency, with or without urge incontinence usually with frequency and nocturia. It causes sudden and unstoppable need to urinate (urinary urgency), even though the bladder may contain a small amount of urine. Overactive bladder, however, should not be considered as normal part of aging.

Overactive bladder is typically caused by spasms of the muscles of the bladder, resulting in an urge to urinate (hence, urge incontinence). It is primarily a problem of the nerves and muscles of the bladder. Voluntary control of the sphincter muscles at the opening of the bladder can hold the urine in the bladder for longer time. Up to 600 cc of urine can be contained in a normal adult bladder. Overactive bladder typically results from inappropriate contraction of the detrusor muscle regardless of the amount of urine. Detrusor is one of the major muscles of the bladder. Its contraction in response to filling of the bladder by urine is one of the steps in the normal process of urination. The contraction and relaxation of the detrusor muscle is regulated by the nervous system. Approximately 300 cc of urine in the bladder can signal the nervous system to trigger muscles of the bladder to coordinate urination.

OAB affects approximately 17% of adults globally. A recent study using current ICS definitions of OAB found the prevalence of OAB to be 11% in men and 13% in women.[28]

1.9.2 Causes of overactive bladder

The common abnormalities of the nervous system that cause overactive bladder are as follows

- Spinal cord injury
- Strokes

- Parkinson’s disease
- Dementia
- Multiple sclerosis

There are also some causes of overactive bladder and urge incontinence with a normal nervous system. For example, urinary tract infection, bladder stones, or bladder tumors can cause also cause over activity of the detrusor muscle, leading to overactive bladder.

1.10 Drugs used to treat overactive bladder: [28]

Antimuscarinic agents are widely used to treat overactive bladder. Some of the antimuscarnic drugs used to treat this condition are:

Oxybutinin

Atropine

Tolterodine tartrate

Ipratropium etc.

CHAPTER-2

LITERATURE REVIEW

2.1 Review of literature:

Kreder *et al(2002).* Reported on longterm safety, tolerability and efficacy of extended release tolterodine in the treatment of overactive bladder. They conducted randomized double blind study in 1377 patients and compared extended release and immediate release dosage forms. They reported that tolterodine ER 4mg displayed a favourable safety, tolerability and efficacy profile during 12 months treatment of patients with overactive bladder .[33]

Vinay pandit *et al.(2008)* studied formulation and evaluation of transdermal films for the treatment of overactive bladder. A number of the polymers like HPMC, carbopol-934p and ethylcellulose were employed alone or in combination for the preparation of transdermal films. The films were casted using solvent casting technique. Solutions containing polymer at different concentrations and polymer at various concentrations were prepared and evaluated for *in vitro* drug release. It was found that polymer concentration of 2% was found to be best and if increased drug release was retarded and 20% concentration of propylene glycol (plasticizer) shows less release. Among all the formulation using HPMC: Carbopol (3:1) with 30% propylene glycol showed the best release.[30]

Lighang zhao *et al(2008).* Examined the transdermal delivery potential of tolterodine using o - acymenthol derivatives as the permeation enhancers as well as correlated the enhancing activity

under *in vitro* and *in vivo* conditions. From the results of *in vitro* and *in vivo* studies it was concluded that (E)-2 isopropyl methylcyclohexyloctadec-9 -enoate(M-OA) is the most promising enhancer among O-acyl menthol derivatives for transdermal drug delivery and 2-isopropyl-5-methyl-cyclohexyl 2-hydroxypanoate (M-LA) produced highest enhancing activity in TOL in isopropylmyristate solution.[31]

Kang ten gong *et al.(2008)* investigated the relationship between formulation variables and drug release in aqueous ethyl cellulose coating. Here they studied on the critical factors and their influence on the drug release characteristics from an aqueous ethylcellulose barrier membrane coated system. It was concluded that the incorporation of HPMC or PVA has shown to be effective in modifying the drug release characteristics through a surelease barrier membrane system. They also reported that by controlling the critical variables like pore former concentration, coating level and drug solubility the desired release characteristic can be achieved .[35]

Maria A.F.H *et al.(2010)* investigated release mechanisms of theophylline pellets coated with aqueous ethylcellulose dispersions containing plasticizers and hydroxyl propyl methylcellulose as a water soluble pore former. Three different release mechanisms of pellets coated with aqueous ethylcellulose dispersion, hydroxypropyl methylcellulose and triethylcitrate, diethyl phthalate, dibutyl phthalate or dibutyl sebacate are determined. It was found that the drug release is dependent on the physical state of swollen ethylcellulose and migration of water soluble pore former respectively.[34]

Fengying S. *et al.(2010)* Prepared and characterized tolterodine PLGA microspheres and carried out pharmacological evaluation to investigate their potential pharmacokinetic and

pharmacodynamic advantage over tolterodine l-tartarate tablets. They reported that the continued inhibition of muscarinic receptor of the microspheres formulation might provide a more effective treatment of OAB patient than that of the oral formulation which inhibits the receptor impulsively.[32]

Namrata et al**.** (2012) In recent pharmaceutical applications, multiparticulate dosage forms are gaining much importance over single-unit dosage forms. The purpose of designing multiparticulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulation and yet devoid of the danger of alteration in drug release profile and formulation behavior due to unit to unit variation. The aim of present work is qualitative study on formulation of multiparticulate modified release pellets of Tolterodine Tartrate, by "*Wurster Based Fluidized Bed Coating Process*"(layering technique).The main purpose of the present study was to investigate the feasibility of the wurster process for preparing extended release pellets and subsequently comparing the release profile of the pellets so prepared with a marketed reference product in various media. Additionally, the effects of some independent process variables were evaluated. The effect of the various process parameters i.e. inlet air temperature, product temperature, exhaust temperature, atomization speed, spray pump speed, atomization air volume and air flow on the Wurster process was studied. The results suggested that the process parameters greatly vary with the physical properties of the drug, polymers and solvents used in process for layering of pellets. [36]

CHAPTER-3

SCOPE, OBJECTIVE AND PLAN OF WORK

3.1 Scope of Work

Tolterodine tartrate is an antispasmodic used in the treatment of bladder hyperactivity. It controls bladder incontinence by controlling contractions. Tolterodine tartrate is a muscuranic receptor antagonist inhibiting bladder contraction and reducing urinary frequency. The contraindication factor that prohibit its use include known hypersensitivity, uncontrolled narrow-angle glaucoma, urinary retention, and gastric retention.

Tolterodine is rapidly absorbed. Both Tolterodine and the 5-hydroxymethyl metabolite reach maximal serum concentrations 1-3 hours after dose. The half-life for Tolterodine given as the tablet is 2-3 hours in extensive metabolizers and about 10 hours in poor metabolizers (devoid of CYP2D6). Steady state concentrations are reached within 2 days after administration of the tablets. Food does not influence the exposure to the sum of the unbound Tolterodine and the active 5-hydroxymethyl metabolite in extensive metabolizers, although the Tolterodine levels increase when taken with food

The recommended dose is 2 mg b.i.d. In the case of troublesome side-effects the dose may be reduced from 2 mg to 1 mg b.i.d. The recommended dose is 1 mg b.i.d. for patients with impaired renal function, impaired liver function, or receiving concomitant ketoconazole or other

potent CYP3A4 inhibitors. Tolterodine tartrate is available in market in 1mg and 2mg as immediate release and 2mg & 4mg as sustained release.

Hence, in the present study, an attempt has been made to develop the sustained-release Capsules of Tolterodine tartrate using hydrophobic ethyl cellulose polymer with the addition of a pore former and a barrier membrane coating and evaluated by in-vitro drug release which will be comparable to the reference product (Detrol, mfg by Pfizer). The drug release data were plotted using various kinetic equations (first-order, Higuchi's kinetics) to evaluate the drug release mechanism and kinetics. In-vivo drug release, biopharmaceutical evaluation, and in-vitro/in-vivo correlations were beyond the scope of this study and will be considered in future work.

3.2 Objective

- The objective of the present work is to prepare the tolterodine tartrate sustained release capsules which matches to the reference product

- To study the effect of different concentration of ethyl cellulose in modifying the drug release and identify the prototype which matches to the originator.

3.3 PLAN OF WORK

3.3.1 Preformulation Study:

a) API Characterisation.

b) Drug- Excipient Compatibility Study.

3.3.2 Formulation Development:

a) Dispensing

b) Preparation of Drug Solution

c) Drug Layering Process (FBP)

d) Film Coating(FBP)

- Preparation of Film Coating Solution
- Coating Process

e) Coating (FBP)

- Preparation of Coating Solution
- Coating Process

f) Sifting

g) Capsule Filling

3.3.3 Evaluation

a) Evaluation Tests For Drug Loaded Tolterodine Tartrate Pellets

- Physical Description
- Sieve Analysis
- Water content by KF titration

b) Evaluation Tests For Capsule Containing Pellets

- Weight Variation Tests
- Content Uniformity
- Lock Length
- Assay by HPLC
- Dissolution by HPLC

3.3.4 Stability studies

CHAPTER-4

MATERIALS AND EQUIPMENTS

4.1 Instruments and Equipments Used

S.No.	**Instruments**	**Make and Model**
1.	Weighing balance	Sartorius(CP225D)
2.	Mechanical stirrer	Vision labs
3.	Tapped density apparatus	Electro lab (ETD-1020)
4.	Fluidized bed processor	Umang
5.	Dissolution test system	Electrolab
6.	HPLC	Shimadzu(LC2010CH)
7.	Automatic capsule filling machine	Rimek formulations
8.	IR Spectroscopy	Bruker

Table:4 List of instruments/equipments used

4.2 LIST OF MATERIALS USED

S.No	Ingredients	Manufacturer
1	Sugar spheres	Degussa, Mumbai
2	**Tolterodine Tartrate**	Rachem pharma ltd
3	HPMC 6cps	Colorcon Asia Pvt Ltd, Goa
4	Talc	Luzenac Pharma, Italy
5	Ethyl Cellulose N-50	Colorcon Asia Pvt Ltd, Goa
6	PVP K30	ISP
7	PEG 6000	Clariant Inc, USA
8	Isopropyl alcohol	Rachem pharma ltd
9	Purified water	Rachem pharma ltd

Table: 5 List of Materials used

4.3 Drug profile: [28]

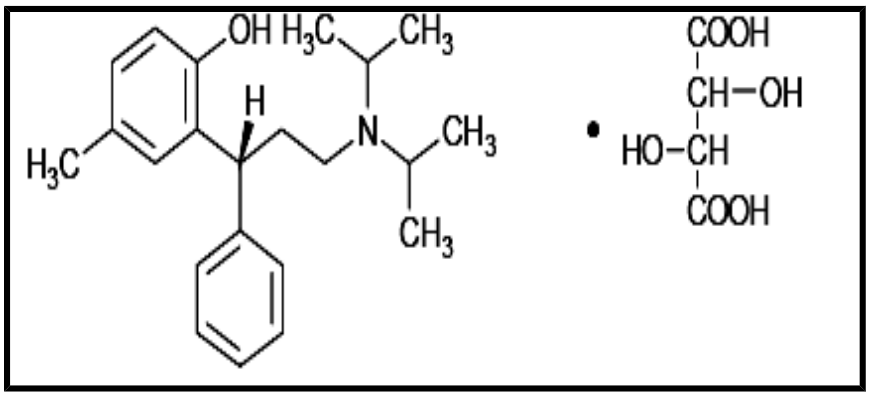
Generic Name: Tolterodine tartarate

Chemical Name: (R)-N,N-diisopropy-3-(2-hydroxy-5-methylphenyl)-3-phenyl propanamine hydrogen tartrate

Chemical Formula: $C_{26}H_{37}NO_7$

Molecular weight: 475.6 gm/mol

Structure of Tolterodine tartrate:



Category: Competitive muscarinic receptor antagonist.

Solubility: Very soluble in water, soluble in methanol, slightly soluble in ethanol, and practically insoluble in toluene.

Melting Point: 205° C

Mechanism of action: Tolterodine is a competitive muscarinic receptor antagonist. Both urinary bladder contraction and salivation are mediated via cholinergic muscarinic receptors. After oral administration, tolterodine is metabolized in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically active metabolite. The 5-hydroxymethyl

metabolite, which exhibits an anti-mucarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect.

Pharmacokinetics: [20,21,28]

Tolterodine is rapidly absorbed. Both tolterodine and the 5-hydroxymethyl metabolite reach maximal serum concentrations 1-3 hours after dose. The half-life for tolterodine given as the tablet is 2-3 hours in extensive metabolizers and about 10 hours in poor metabolizers (devoid of CYP2D6). Steady state concentrations are reached within 2 days after administration of the tablets. Food does not influence the exposure to the sum of the unbound tolterodine and the active 5-hydroxymethyl metabolite in extensive metabolizers, although the tolterodine levels increase when taken with food. Clinically relevant changes are likewise not expected in poor metabolizers.

Absorption:

After oral administration tolterodine is subject to CYP2D6 catalyzed first-pass metabolism in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically active metabolite. The absolute bioavailability of tolterodine is 17% in extensive metabolizers, the majority of the patients, and 65% in poor metabolizers (devoid of CYP2D6).

Distribution:

Tolterodine and the 5-hydroxymethyl metabolite bind primarily to alpha-1-acid glycoprotein. The unbound fractions are 3.7% and 36%, respectively. The volume of distribution of tolterodine is 113 L.

Metabolism:

Tolterodine is extensively metabolized by the liver following oral dosing. The primary metabolic route is mediated by the polymorphic enzyme CYP2D6 and leads to the formation of the 5-hydroxymethyl metabolite. The half-life of the 5-hydroxymethyl metabolite is 3-4 hours. Further metabolism leads to formation of 5-carboxylic acid and N-dealkylated 5-carboxylic acid metabolites, which account for 51 % and 29 % of the metabolites recovered in the urine, respectively. A subset (about 7%) of the population is devoid of CYP2D6 activity. The identified pathway of metabolism for these individuals (poor metabolizers) is de-alkylation via CYP3A4 to N-dealkylated tolterodine, which does not contribute to the clinical effect. The remainder of the population is referred to as extensive metabolizers. The systemic clearance of tolterodine in extensive metabolizers is about 30 L/h. In poor metabolizers the reduced clearance leads to significantly higher serum concentrations of tolterodine (about 7-fold) and negligible concentrations of the 5-hydroxymethyl metabolite are observed.

The 5-hydroxymethyl metabolite is pharmacologically active. Because of the differences in the protein-binding characteristics of tolterodine and the 5-hydroxymethyl metabolite, the exposure (AUC) of unbound tolterodine in poor metabolizers is similar to the combined exposure of unbound tolterodine and the 5-hydroxymethyl metabolite in patients with CYP2D6 activity given the same dosage regimen. The safety, tolerability and clinical response are similar irrespective of phenotype.

Elimination:

The excretion of radioactivity after administration of 14C-tolterodine is about 77% in urine and 17% in faeces. Less than 1% of the dose is recovered as unchanged drug, and about 4% as the 5-hydroxymethyl metabolite. The carboxylated metabolite and the corresponding dealkylated metabolite account for about 51% and 29% of the urinary recovery, respectively.

Indications and usage:

Tolterodine tartrate is indicated for the treatment of overactive bladder with symptoms of urinary urgency, frequency and/or urge incontinence.

Dosage and administration:

The recommended dose is 2 mg b.i.d. In the case of troublesome side-effects the dose may be reduced from 2 mg to 1 mg b.i.d. The recommended dose is 1 mg b.i.d. for patients with impaired renal function, impaired liver function, or receiving concomitant ketoconazole or other potent CYP3A4 inhibitors. After six months the need for further treatment should be considered. Safety and effectiveness in children have not been established.

Contraindications:

Tolterodine is contraindicated in patients with:

- Known hypersensitivity to Tolterodine or any other component of the drug.
- Urinary retention
- Uncontrolled narrow angle glaucoma.

Warning and Precautions:

Tolterodine Tartrate should be used with caution in following patients:

- At risk for urinary retention.
- At risk for decreased gastro intestinal motility.
- With impaired renal function.
- With impaired hepatic function
- With myasthenia gravis.

Storage:

Store in a tightly closed container.

4.4.EXCIPIENT PROFILE[17,18]

4.4.1. Ethyl cellulose

Nonproprietary Names

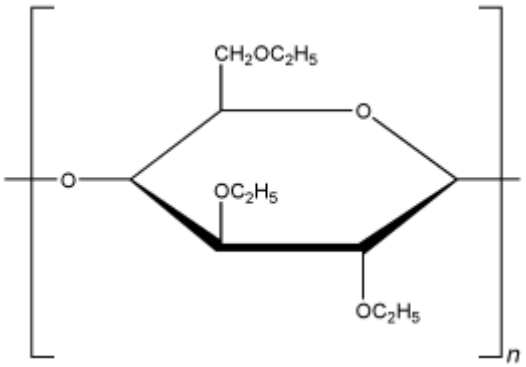
- BP: Ethyl cellulose
- PhEur: Ethyl cellulosum
- USPNF: Ethyl cellulose
- Synonyms: Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.

Chemical Name: Cellulose ethyl ether

Empirical Formula and Molecular Weight: Ethylcellulose with complete ethoxyl substitution (DS = 3) is

$C_{12}H_{23}O_6(C_{12}H_{22}O_5)_nC_{12}H_{23}O_5$ where *n* can vary to provide a wide variety of molecular weights. Ethyl cellulose, an ethyl ether of cellulose, is a long-chain polymer of β-anhydroglucose units joined together by actual linkages.

Structural Formula



Functional Category: Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity-increasing agent.

Description: Ethyl cellulose is a tasteless, free-flowing, white to light tan-colored powder.

Applications in Pharmaceutical Formulation or Technology: Ethyl cellulose is widely used in oral and topical pharmaceutical formulations;

Table 6 : Uses of Ethyl cellulose.

Use	**Concentration (%)**
Microencapsulation	10.0–20.0

Use	Concentration (%)
Sustained-release tablet coating	3.0–20.0
Tablet coating	1.0–3.0
Tablet granulation	1.0–3.0

- ✓ The main use of ethyl cellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethyl cellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethyl cellulose to inhibit oxidation. Modified-release tablet formulations may also be produced using ethyl cellulose as a matrix former.

- ✓ Ethyl cellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films. Higher-viscosity ethyl cellulose grades tend to produce stronger and more durable films. Ethyl cellulose films may be modified to alter their solubility, by the addition of hypromellose or a plasticizer; An aqueous polymer dispersion (or latex) of ethyl cellulose such as *Aquacoat ECD* (FMC Biopolymer) or *Surelease* (Colorcon) may also be used to produce ethyl cellulose films without the need for organic solvents.

- ✓ Drug release through ethylcellulose-coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g. pellets or granules compared with tablets) is utilized. In those instances, aqueous ethyl cellulose dispersions are generally used to coat granules or pellets. Ethyl cellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression.

- ✓ High-viscosity grades of ethyl cellulose are used in drug microencapsulation.

- ✓ Release of a drug from an ethyl cellulose microcapsule is a function of the microcapsule wall thickness and surface area.

- ✓ In tablet formulations, ethyl cellulose may additionally be employed as a binder, the ethyl cellulose being blended dry or wet-granulated with a solvent such as Ethanol (95%). Ethyl cellulose produces hard tablets with low friability, although they may demonstrate poor dissolution.

- ✓ Ethyl cellulose has also been used as an agent for delivering therapeutic agents from oral (e.g. dental) appliances.

In topical formulations, ethyl cellulose is used as a thickening agent in creams, lotions, or gels, providan appropriate solvent is used. Ethyl cellulose has been studied as a stabilizer for emulsions. [17,18]

4.4.2. Hypromellose

Nonproprietary Names:

- BP: Hypromellose
- JP: Hydroxypropylmethylcellulose
- PhEur: Hypromellosum
- USP: Hypromellose

Synonyms:

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.

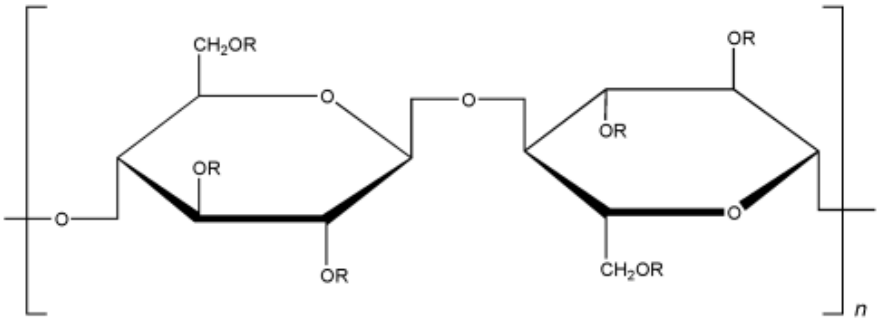
Chemical Name:

Cellulose hydroxypropyl methyl ether

Empirical Formula and Molecular Weight:

Hypromellose defined in the USP 28 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group ($OCH_2CH(OH)CH_3$), calculated on a dried basis.. Molecular weight is approximately 10 000–1 500 000. The JP 2001 includes three separate monographs for hypromellose: hydroxypropylmethylcellulose 2208, 2906, and 2910, respectively.

Structural Formula:



Where R is H, CH_3, or $CH_3CH(OH)CH_2$

Functional Category:

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology:

- ✓ Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.

- ✓ In oral products, Hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.

- ✓ Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-

coating solutions, while higher-viscosity grades are used with organic solvents. Examples of film-coating materials that are commercially available include *AnyCoat C*, *Spectracel*, and *Pharmacoat*.

- ✓ Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

- ✓ Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

- ✓ In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Description:

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.[17,18]

4.4.3.IPA

Nonproprietary Names:

- BP: Isopropyl alcohol
- JP: Isopropanol

- PhEur: Alcohol isopropylicus
- USP: Isopropyl alcohol

Synonyms:

Dimethyl carbinol; IPA; isopropanol; petrohol; 2-propanol; *sec*-propyl alcohol.

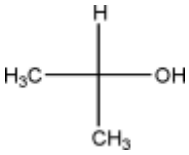
Chemical Name:

Propan-2-ol

Empirical Formula and Molecular Weight:

C_3H_8O,60.1

Structural Formula:



Functional Category:

Disinfectant; solvent.

Applications in Pharmaceutical Formulation or Technology:

- ✓ Isopropyl alcohol (propan-2-ol) is used in cosmetics and pharmaceutical formulations primarily as a solvent in topical formulations. It is not recommended for oral use owing to its toxicity;

- ✓ Although it is used in lotions, the marked degreasing properties of isopropyl alcohol may limit its usefulness in preparations used repeatedly. Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation, where the isopropyl alcohol is subsequently removed by evaporation. It has also been shown to significantly increase the skin permeability of nimesulide from carbomer 934.

- ✓ Isopropyl alcohol has some antimicrobial activity and a 70% v/v aqueous solution is used as a topical disinfectant. Therapeutically, isopropyl alcohol has been investigated for the treatment of postoperative nausea or vomiting.

Description:

Isopropyl alcohol is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor resembling that of a mixture of Ethanol and acetone; it has a slightly bitter taste.[17,18]

4.4.4. PEG

Nonproprietary Names:

- BP: Macrogols
- JP: Macrogol 400

- Macrogol 1500
- Macrogol 4000
- Macrogol 6000
- Macrogol 20000
- PhEur: Macrogola
- USPNF: Polyethylene glycol

Synonyms:

Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; PEG; PluriolE;polyoxyethylene glycol.

Chemical Name:

α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl) [25322-68-3]

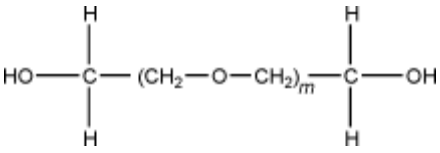
Empirical Formula and Molecular Weight:

$HOCH_2(CH_2OCH_2)_mCH_2OH$ where *m* represents the average number of oxyethylene groups.

Alternatively, the general formula $H(OCH_2CH_2)_nOH$ may be used to represent polyethylene glycol, where *n* is a number *m* in the previous formula + 1.

The number that follows PEG indicates the average molecular weight of the polymer.

Structural Formula:



Functional Category:

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology:

- ✓ Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations. It has been used experimentally in biodegradable polymeric matrices used in controlled-release systems.

- ✓ Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin; They do not readily penetrate the skin, although the polyethylene glycols are water-soluble and are easily removed from the skin by washing, making them useful as ointment bases. Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol.

- ✓ Mixtures of polyethylene glycols can be used as suppository bases, for which they have many advantages over fats. For example, the melting point of the suppository can be made higher to withstand exposure to warmer climates; release of the drug is not dependent upon melting point; the physical stability on storage is better; and suppositories are readily miscible with rectal fluids. Polyethylene glycols have the following disadvantages: they are chemically more reactive than fats; greater care is needed in processing to avoid inelegant contraction holes in the suppositories; the rate of release of water-soluble medications decreases with the increasing molecular weight of

the polyethylene glycol; and polyethylene glycols tend to be more irritating to mucous membranes than fats.

- ✓ Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers.

- ✓ Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential absorption of moisture from gelatin in the shell.

- ✓ In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.

Description:

Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures.

Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders. [17,18]

4.4.5. Talc

Nonproprietary Names

- BP: Purified talc
- JP: Talc
- PhEur: Talcum
- USP: Talc

Synonyms

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Puretalc; soapstone; steatite; Superiore.

Chemical Name

Talc

Empirical Formula and Molecular Weight

Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

Functional Category

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Table 7: Uses of talc

Use	**Concentration (%)**
Dusting powder	90.0–99.0
Glidant and tablet lubricant	1.0–10.0
Tablet and capsule diluent	5.0–30.0

- ✓ Although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbant.

- ✓ In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves; Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder.

- ✓ Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

Description

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness. [17,18]

4.4.6. Sugar Spheres

Nonproprietary Names

- BP: Sugar spheres
- PhEur: Saccharispheri
- USPNF: Sugar spheres

Synonyms

Non-pareil; non-pareil seeds; NPTAB; Nu-Core; Nu-Pareil PG; sugar seeds; Suglets.

Functional Category

Tablet and capsule diluent.

Applications in Pharmaceutical Formulation or Technology

- ✓ Sugar spheres are mainly used as inert cores in capsule and tablet formulations, particularly multiparticulate sustained-release formulations. They form the base upon which a drug is coated, usually followed by a release-modifying polymer coating.

- ✓ Alternatively, a drug and matrix polymer may be coated onto the cores simultaneously. The active drug is released over an extended period either via diffusion through the polymer or through to the controlled erosion of the polymer coating.

- ✓ Complex drug mixtures contained within a single-dosage form may be prepared by coating the drugs onto different batches of sugar spheres with different protective polymer coatings.

- ✓ Sugar spheres are also used in confectionery products.

Description

The USPNF 23 describes sugar spheres as approximately spherical granules of a labeled nominal-size range with a uniform diameter and containing not less than 62.5% and not more than 91.5% of sucrose, calculated on the dried basis. The remainder is chiefly starch.

The PhEur 2005 states that sugar spheres contain not more than 92% of sucrose calculated on the dried basis. The remainder consists of corn (maize) starch and may also contain starch hydrolysates and color additives. The diameter of sugar spheres varies from 200 to 2000 μm and the upper and lower limits of the size of the sugar spheres are stated on the label. [17,18]

4.4.7. Water

Nonproprietary Names

- BP: Purified water
- JP: Purified water
- PhEur: Aqua purification
- USP: Purified water

Synonyms

Aqua; hydrogen oxide.

Chemical Name

Water

Empirical Formula and Molecular Weight

H_2O, 18.02

Functional Category

Solvent.

Applications in Pharmaceutical Formulation or Technology

- ✓ Water is the most widely used excipient in pharmaceutical production operations. Specific grades of water are used for particular applications in concentrations up to 100%

Table 8 : Applications of specific grades of water.

Type	Use
Bacteriostatic water for injection	Diluent for ophthalmic and multiple-dose injections.
Potable water	Public supply suitable for drinking, the purity of which is unlikely to be suitable for use in the manufacture of pharmaceuticals.
Purified water	Vehicle and solvent for the manufacture of drug products and pharmaceutical preparations; not suitable for use in the manufacture of parenteral products.
Sterile water for inhalation	Diluent for inhalation therapy products.
Sterile water for injection	Diluent for injections.

Type	Use
Sterile water for irrigation	Diluent for internal irrigation therapy products.
Water for injections in bulk	Water for the bulk preparation of medicines for parenteral administration.

- ✓ Purified water and water for injection are also used for cleaning operations during production of pharmaceutical products.

Description

The term ‘water’ is used to describe potable water that is freshly drawn direct from the public supply and is suitable for drinking. The chemical composition of potable water is variable and the nature and concentrations of the impurities in it depend upon the source from which it is drawn. Although potable water must be both palatable and safe to drink, for most pharmaceutical applications potable water is purified by distillation, ion exchange treatment, reverse osmosis, or some other suitable process to produce ‘purified water’. For certain applications, water with pharmacopeial specifications differing from those of purified water should be used, e.g. water for injection; Water is a clear, colorless, odorless, and tasteless liquid.

CHAPTER-5

METHADOLOGY

5.1. Analytical Method Development

5.1.1. Scanning of λ max:

Preparation of stock solution (1mg/ml): 100mg of Tolterodine was dissolved in 10ml of methanol in a 100ml standard flask and this solution was made upto 100ml with methanol.

For the selection of analytical wavelength, 10 µg/ml solution of Tolterodine was prepared by appropriate dilution of standard stock solution and scanned in the spectrum mode from 200 nm to 400 nm.

5.1.2. Preparation of standard curve:

The standard curve was established by preparing a stock solution(1mg/ml). 100mg of Tolterodine was dissolved in 10ml of methanol in a 100ml standard flask and this solution was made upto 100ml with methanol. From the stock solution 10ml solution was transferred to a 100ml standard flask and volume was made upto 100ml with methanol.

From the above prepared solution 10ml was transferred to a 100ml standard flask and volume was made upto 100ml with methanol. This was used as the working stock solution. From the working stock solution different concentrations ranging between 5 to 25 µg/ml were prepared. Absorbance was determined by using UV spectrophotometer.

From this data, the standard curve of Tolterodine was obtained by plotting absorbance on Y-axis against concentration on X-axis.

5.2. Preformulation Studies

5.2.1 API Characterization:

The overall objective of preformulation testing is to generate information useful in developing the formulation which is stable and bioavailable. Further the use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product. For any drug substance to formulate into a dosage form, it is necessary to study the physicochemical properties of the bulk drug like physical appearance, solubility, melting point, particle size, compatibility.

5.2.1.a. Physical Appearance:

The appearance of the API was done by visual observation. The content was observed visually for compliance against the specification.

5.2.1.b.Solubility Studies:

The solubility of drug is an important physicochemical property because it affects the bioavailability of the drug, the rate of drug release into the dissolution medium, and consequently the therapeutic efficacy of the pharmaceutical product. The solubility of a material is usually determined by the equilibrium solubility method, which employs a saturated solution of the material, obtained by stirring an excess of material in the solvent for a prolonged period until equilibrium is achieved.

5.2.1.c.Sieve Analysis:

The main aim of sieve analysis is to determine the different size of drug particles present. A series of standard sieve are stacked one above the other so that sieves with larger pore size (less

sieve number) occupy top position followed by sieves with smaller pore size (greater sieve number towards the bottom).

Procedure:

A series of sieves were arranged in the order of their decreasing pore diameter (increasing sieve number) such as sieve number 20, 30, 40, 60, 100 and 200. 100 grams of drug was weighed accurately and transferred to sieve number 20 which were kept on top. The sieves were shaken for about 5-10 minutes. Then the drug retained on each sieves was taken, weighed separately and amount retained was expressed in terms of percentage.

5.2.2. Drug - Excipient Compatibility Studies:

Compatibility studies were carried out to study the possible interactions between Tolterodine Tartrate and other inactive ingredients.

Procedure:

The compatibility studies were carried out by taking a mixture of drug and excipients at the ratio in which they are expected to be present in the innovator product. A part of mixture was exposed to different storage conditions like 40 ºC±2ºC /75% RH ±5% RH and control samples were kept at 2-8 ºC. They were tested with respect to their physical and chemical aspects. These samples were collected at regular intervals and subjected to Differential Scanning Calorimetry.

Table 9: Conditions for compatibility studies

S.No.	Storage Condition	Samples packed in	Sampling Periods
1	Accelerated 40 °C±2°C /75% RH ±5% RH	3 Double polythene bags	1, 2, 3, 4 Weeks
2	Refrigeration 2-8°C	1 Double polythene bag + 1 glass vessel	1, 2, 3, 4 Weeks

FT-IR Spectrophotometric Method:

Potassium Bromide (KBr) pellet method was employed . KBr was dried in oven at 45 °C before analysis. The pure drug was triturated with KBr and pellet was prepared by setting the pressure to 100 kg/cm^2 for 2 minutes. The obtained pellet was analyzed in FTIR 8400 S, Shimadzu, Japan. KBr background was obtained initially before analysis of test samples. The same procedure was repeated for analysis of drug and HPMC E5, HPMC K4M, also drug and excipient mixture free from moisture content were used for analysis.[37]

5.3 Method of Manufacture[8, 15, 22]

Dispensing

The dispensing of Active Pharmaceutical Ingredient and Excipients is carried out as per the manufacturing formula.

Preparation Of Drug Solution :

Disperse Tolterodine Tartrate in purified water continuous stirring till a uniform suspension is obtained. Hypromellose and talc were dissolved in purified water and stirred until a clear solution is obtained. HPMC and talc solution was transferred into the drug solution and were continuously stirred until a uniform suspension was obtained.

Drug Layering Process (FBP)

Sugar spheres (20#-25#) were loaded into FBP bowl. The sugar spheres were coated by bottom spray wruster at peristaltic pump rpm of 25-100 and atomizing air pressure of 2.0-5.0 Kg/cm^2 till the coating solution was completed. The drug solution was sprayed completely and after the completion of drug solution the fluidization level was reduced and drying was done for 10-15 minutes. The drug layered pellets were unloaded from FBP, sifted and readied for Film coating.

Barrier Coating (FBP) [23,25]

Preparation Of Barrier Coating Solution:

Hypromellose was dissolved in purified water with continuous stirring until a uniform solution was obtained.

Coating Process

The drug loaded pellets (18#-20#) were loaded into FBP bowl. The drug loaded pellets were coated by bottom spray wruster at peristaltic pump rpm of 15-20 and atomizing air pressure of 2.0-5.0 Kg/cm^2 till the coating solution was completed. The coating solution was sprayed completely and after the completion of drug solution the fluidization level was reduced and drying was done for 10-15 minutes. The drug layered pellets were unloaded from FBP, sifted and readied for EC coating.

SR Coating (FBP)

Preparation Of Coating Solution :

Ethyl cellulose, Povidone and Talc were dispersed in Isopropyl Alcohol with continuous stirring till a uniform suspension was obtained. Polyethylene glycol was dissolved in purified water and stirred to get a clear solution. The EC solution was transferred into the PEG in water solution and was continuously stirred until a uniform suspension was obtained.

Coating Process

The drug loaded pellets (18#-20#) were loaded into FBP bowl. The drug loaded pellets were coated by bottom spray wruster at peristaltic pump rpm of 15-20 and atomizing air pressure of 2.0-5.0 Kg/cm^2 till the coating solution was completed. The coating solution was sprayed completely and after the completion of drug solution the fluidization level was reduced and drying was done for 10-15 minutes. The drug layered pellets were unloaded from FBP and were sifted prior to be filled in capsules.

Sifting

Sift the coated dried pellets through the #18 and collect retains and downs separately.

Sift the #18 passing pellets through #20 and collect retains and passing separately

Capsule Filling

The fill weight of 200 mg is checked and filled in size “3”capsule in the capsule filling machine.

Table 10: FBP parameters

S.No.	Parameters	Specifications
1	Atomizing air pressure (kg/cm^2)	2.0-5.0
2	Inlet temperature (°c)	(40-50)
3	Bed temperature (°c)	(40-45)
4	Peristaltic pump rpm	25-100

S.No	Ingredients(mg)	Quantity							
		Trial I	**Trial II**	**Trial III**	**Trial IV**	**Trial V**	**Trial VI**	**Trial VII**	**Trial VIII**
Drug Loading									
1	Sugar Spheres	171	172	174	170	171	171	171	174
2	**Tolterodine Tartrate**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
3	HPMC	6	6	6	6	6	6	6	6

	6cps								
4	Talc	2	2	2	2	2	2	2	2
5	Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Barrier Coating									
6	HPMC 6cps	---	---	---	5.5	5	4.5	4	3
7	Purified water	---	---	---	Q.S	Q.S	Q.S	Q.S	Q.S
SR Coating									
8	Ethyl Cellulose N-50	12	11	9	8	7.5	7	6.5	6
9	PVP K30	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
10	PEG 6000	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
11	Talc	2	2	2	2	2	2	2	2
12	IPA	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
13	Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

TABLE 11 : Formulation of Tolterodine Tartrate Core Pellets

5.4. Evaluation

A. Evaluation Tests For Drug Loaded Tolterodine Tartrate Pellets:

5.4.1. Physical Description:

0.5g of pellets were transferred into a dry petri dish or dispensed on a white card. The content was visually observed for compliance against specification.

5.4.2. Sieve Analysis:

The particle size of the pellets after drug loading wass evaluated by mechanical sieving using a series of sieves with aperture size 1, 0.85, 0.71, 0.60mm. A sample load of 100g was placed on the sieve and shaken by mechanical shaker. The weight of pellets retained on each sieve was determined and mean particle size was determined.

5.4.3. Water Content by KF Titration:

30ml of methanol was taken in a clean, dried Karl Fischer titration flask and titrated with KF reagent until the end point to neutralize the free water. Tolterodine Tartrate pellets were powdered finely. Accurately weighed quantity of 0.5gm of sample was transferred to the titration flask and dissolved by stirring and titrated with KF reagent to the end point and percentage water content was calculated by following formula.

$$\% \text{ Water Content} = V \times F \times 100 / W \times 100$$

Where, V = Volume of KF reagent consumed by sample

F = Factor for KF reagent

W = Weight of sample in grams.

B. Evaluation Tests For Capsules Containing Pellets:

5.4.4. Weight Variation Test:

20 intact capsules were selected randomly and weighed and average weight was calculated. Individual weight of each capsule was determined. According to USP, none of the individual capsule weight should be less than 90% and more than 110% of the average weight.

5.4.5. Content Uniformity:

According to USP, 30 intact capsules were selected, of which 10 were assayed. 9 of 10 capsules should be within the potency range of 85%-115%. The potency of 10^{th} capsule should not exceed the range of 75-125%.

5.4.6. Lock Length:

The lock length can be determined by vernier callipers. The empty capsule cap and body were measured individually to know the lock length of the capsule.

5.4.7. Assay by HPLC :

Reagents:

Potassium dihydrogen orthophosphate : AR Grade

Triethylamine : AR Grade

Acetonitrile : HPLC Grade

Methanol : HPLC Grade

Water : Milli-Q-Grade

Chromatographic Conditions:

Column : Develosil C18, 250mm x 4.6mm x 5µm or its equivalent

Flow Rate : 1.0 ml/min

Wave Length : 215 nm

Column Temperature : 25°C

Injection Volume : 100 µL

Run Time : 12 minutes.

Preparation of Mobile Phase:

About 2.0g of potassium hydrogen phosphate was weighed and dissolved in 425 ml of water. 400 ml of methanol and 175 ml of acetonitrile were added. pH of the solution was adjusted to 7.2 with Triethylamine. Solution was filtered and degassed.

Preparation of Standard Solution:

Accurately weighed quantity of about 25mg of Tolterodine Tartrate working standard was transferred into 50ml volumetric flask. 20 ml of methanol was added and sonicated for 10 minutes and diluted with methanol to make up the volume. It was mixed and filtered. 2 ml of this solution was transferred to a 100ml volumetric flask and diluted with mobile phase to the make up the volume and mixed.

Preparation of Sample Solution:

Accurately weighed quantity of powdered pellets equivalent to 25mg of Tolterodine Tartrate was transferred into 250ml volumetric flask, 150ml of mobile phase was added and sonicated for 30 minutes and solution was cooled to room temperature. This was diluted with mobile phase to make up the volume, mixed and filtered. 5ml of this solution was transferred to 50ml volumetric flask and diluted with mobile phase to make up the volume and mixed.

System Suitability:

The peak responses are recorded for standard preparation and sample preparation. The relative standard deviation for six replicate standard solution injections should not be more than 2%. The tailing factor for Tolterodine Tartrate peak should not be more than 2.0. Theoretical plates for Tolterodine Tartrate peak should not be less than 2000.

Procedure:

100µl, six replicate injections of standard solution and single injection of sample solution were injected. The chromatograms are recorded and the peak response was measured. The assay (in %) was calculated by using following formula.

$$\%\text{Drug Content} = \frac{A_T}{A_S} \times \frac{W_S}{50} \times \frac{2}{100} \times \frac{250}{W_T} \times \frac{50}{5} \times \frac{P}{100} \times \frac{100}{\text{Label claim}} \times 100$$

Where,
A_T = Peak area of Tolterodine Tartrate in sample solution
A_S = Average peak area of Tolterodine Tartrate in standard solution
W_S = Amount of Tolterodine Tartrate taken in working standard (mg)
W_T = Amount of sample (mg)
P = Potency of Tolterodine Tartrate working standard used.

5.4.8. Dissolution by HPLC :

Chromatographic Conditions:

Column : Develosil C18, 250mm x 4.6mm x 5µm or its equivalent

Flow Rate : 1.0 ml/min

Wave Length : 215 nm

Column Temperature : 25°C

Injection Volume : 100 µL

Run Time : 12 minutes.

Dissolution Parameters:

Medium : 900ml of pH 6.8 phosphate buffer

Apparatus : USP Type I (Basket)

RPM : 100

Temperature : 37 ± 0.5ºC

Time Intervals : 1st Hour, 2nd Hour, 4th Hour and 8th Hour.

Preparation of Dissolution medium:

6.8g of potassium hydrogen ortho phosphate was dissolved in 1000ml water. pH was adjusted to 6.8±0.5 with 2N Sodium hydroxide or 2N Hydrochloric acid.

Preparation of Mobile Phase:

2.0g of potassium hydrogen phosphate was weighed and dissolved in 425 ml of water. 400 ml of methanol and 175mL of acetonitrile was added. The pH of the solution was adjusted to 7.2 with Triethylamine, filtered and degased.

Preparation of Standard Solution:

Accurately weighed quantity of about 25mg of Tolterodine Tartrate working standard was transferred into 50ml volumetric flask. 20 ml of methanol was added and sonicated for 10 minutes and diluted with methanol to make up the volume, mixed and filtered. 1 ml of this solution was transferred to a 100ml volumetric flask, diluted with mobile phase to the make up the volume and mixed.

Preparation of Sample Solution:

The pellets equivalent to 4mg of Tolterodine Tartrate were transferred into each of the six dissolution jars and the apparatus was run. At the end of the 1^{st}, 2^{nd}, 4^{th} and 8^{th} hours 10ml of the sample solution were withdrawn from each dissolution jars and same volume was replaced using the prepared medium. Temperature was maintained at 37±0.5℃. The solution was filtered through 0.45µ nylon filter.

Procedure:

100µl of dissolution media, six replicate injections of standard solution and single injection of sample solutions were separately injected into the chromatograph. The chromatograms were recorded and peak responses were measured.

System Suitability:

The peak responses were recorded for standard preparation and sample preparation. The relative standard deviation for six replicate standard solution injections should not be more than 2%. The tailing factor for Tolterodine Tartrate peak should not be more than 2.0. Theoretical plates for Tolterodine Tartrate peak should not be less than 2000.

Calculation:

% labeled amount of Tolterodine Tartrate dissolved

$$\frac{A_T}{A_S} \times \frac{W_S}{50} \times \frac{1}{100} \times \frac{900}{W_T} \times \frac{P}{\%\ \text{Label Claim}} \times 100$$

Where,

A_T = Absorbance of Tolterodine Tartrate sample solution

A_S = Absorbance of Tolterodine Tartrate standard solution

W_S = Weight of Tolterodine Tartrate in working standard(mg)

W_T = Weight of Tolterodine Tartrate pellets taken (mg)

P = Potency of Tolterodine Tartrate working standard used

5.4.9. Dissolution profile comparision using Similarity and Dissimilarity Factors.

f1=Dissimilarity factor

f2=Similarity factor

A dissolution profile characterizes the product more precisely than a single point dissolution test. It helps to assure similarity in product performance and signals bioequivalence. The factor f1 is proportional to the average indifference between two profiles, where as factor f2 inversely proportional to the average squared indifference between two profiles. The factor f2 measures the closeness between two profiles. FDA has set a public standard of f2 value between 50-100 to indicate similarity between two profiles.

$f1 = \Sigma D\ (1/\ \Sigma t)\ 100$

$f2 = 50 \times \ln\{1/❍1+\Sigma\ (Rt-Tt)^2\}$

Procedure: The mean dissolution values of the two profiles (test and innovator) are taken which should be made under same test conditions and same time points. The time points are taken as 1,4,7 hours. The following mathematical approach is made to compare the dissolution profiles of Tolterodine Tartrate pellets using two factors f1 and f2.

5.4.10. Stability Studies

Stability studies are an integral part of the drug development program and are one of the most important areas in the registration of pharmaceutical products. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light and enables recommended storage conditions, re-test periods and shelf half- lives to be established. Stability assessment starts with studies on the substance to determine degradation products, degradation pathway. In these type of studies the pellets are stored in suitable containers and stability study is conducted as per ICH guidelines. The product is analyzed at intervals for various parameters which may include assay of active ingredient, measurement of known degradation products, hardness, disintegration time, dissolution time, appearance, etc., Stability studies have been conducted at following conditions.[27]

Storage conditions:40 ºC ± 2 ºC /75%RH ± 5%RH, 25 ºC ± 2 ºC /60% RH ± 5% RH

Packs: Capsules containing pellets have been packed into blister packages.

CHAPTER-6

RESULTS & DISCUSSION

6. RESULTS & DISCUSSION

6.1. Analytical Method Development:

6.1.1. Scanning of λ max:

For the selection of analytical wavelength, 10 µg/ml solution of Tolterodine was prepared by appropriate dilution of standard stock solution(1mg/ml) and scanned in the spectrum mode from 200 nm to 400 nm.From the spectra of drug λmax of Tolterodine tartrate, 284.5 nm was selected for the analysis.

6.1.2. Preparation of standard curve:

The maximum absorption was observed at 284.5nm. 1mg/ml (1000µg/ml) solution was prepared by dissolving 100mg in 100 ml of Methanol. From the secondary stock (100 µg/ml) 0.5, 1.0, 1.5, 2.0, and 2.5 ml, was taken separately and made up to 10 ml with Methanol to produce 5, 10, 15, 20 and 25 µg/mL respectively. The absorbance was measured at 284.5nm using a UV spectrophotometer.

Table 12: Standard values of Tolterodine Tartrate

Concentration (µg/ml)	Absorbance
0	0
5	0.145
10	0.275
15	0.405
20	0.535
25	0.665

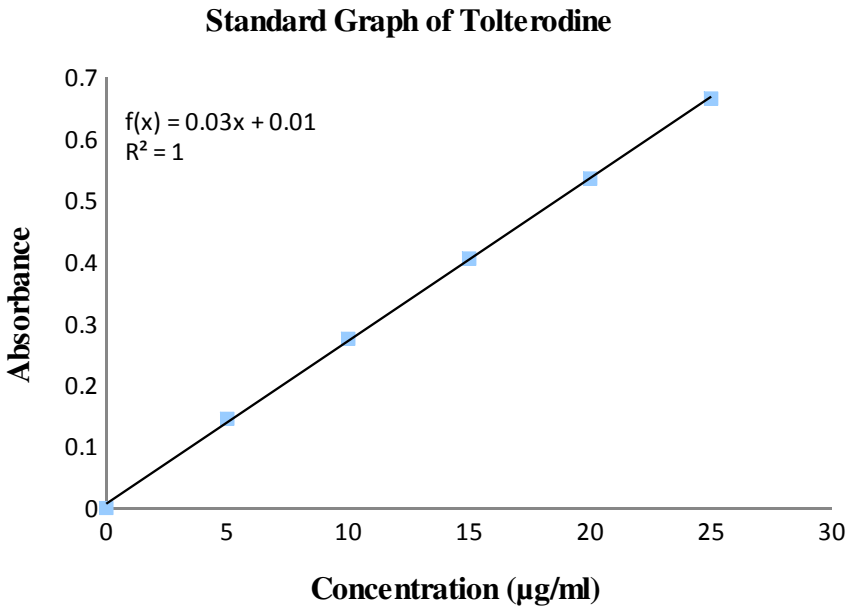


Fig:12 Standard Graph of Tolterodine

6.2. Pre-Formulation Studies:

Table 13: Characterization of Tolterodine tartarate

S.No	Test	Specification	Result
1.	Description	A white or off –white powder	A white or off-white powder
2.	Solubility	Very soluble in water, soluble in methanol, slightly soluble in ethanol and practically insoluble in toluene	Complies
3.	Water content (by Karl-Fisher)	Not more than 0.8%w/w	Complies
4.	LOD	By I.R moisture analyser,105⎫C	≤1.0 % w/w
5.	Assay on anhydrous basis(potentiometric)	<98% and not more than 102%	99.8%w/v
6.	Part size analysis	0.420mm	0.420mm
7.	Melting point	205°C	205°C

Table 14 : Result of preformulation study of Tolterodine tartarate

Parameter	Result
Angle of repose (°)	33
Bulk density (g/cm^3)	0.3
True density(g/cm^3)	0.45
Carr's compressibility index (%)	33.333
Hausner's ratio	1.5

Solubility:

The solubility of the drug was determined by the equilibrium solubility method, which employs a saturated solution of the material, obtained by stirring an excess of material in the solvent, ranging from polar to non-polar for a prolonged period until equilibrium is achieved. It was inferred that 11mg of Tolterodine Tartrate was soluble in 1ml of Water,1mg of Tolterodine Tartrate was soluble in 1ml of Ethanol and Methanol,5.8mg of Tolterodine Tartrate was soluble in 1ml of Oleic acid, 6.69mg of Tolterodine Tartrate was soluble in 1ml of Ethyl acetate.

6.3.1. Physical Compatibility:

Compatibility studies were carried out to study the possible interactions between Tolterodine Tartrate and the polymers used for coating in the formulation. The method employed for the analysis was the KBr pellet method. The mixtures were exposed to different storage conditions and the samples were collected at regular intervals and were tested with respect to their physical and chemical aspects.

Table 15.Physical Compatibility Results

Material	Sample Status After 1 month, kept at Accelerated 40°C±2°C/75% RH±5% RH	Sample Status After 1 month, kept at 25°C ± 2°C /60%RH ± 5% RH
Tolterodine Tartrate	No Change	No Change
Tolterodine Tartrate + HPMC	No Change	No Change
Tolterodine Tartrate + Ethyl Cellulose	No Change	No Change

6.4. FOURIER TRANSFORM INFRARED SPECTROSCOPY

The I.R spectrum of drug alone and with the excipients was observed

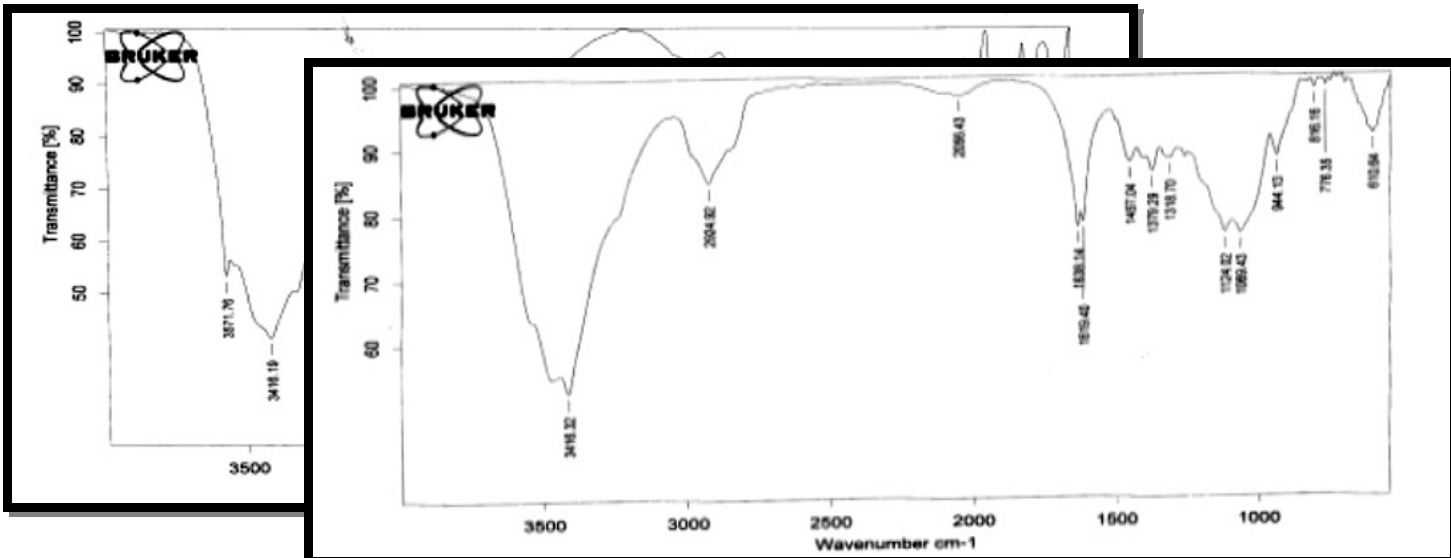


Figure 13 : I.R Spectrum of Drug

Figure 14: I.R Spectrum of Drug + HPMC

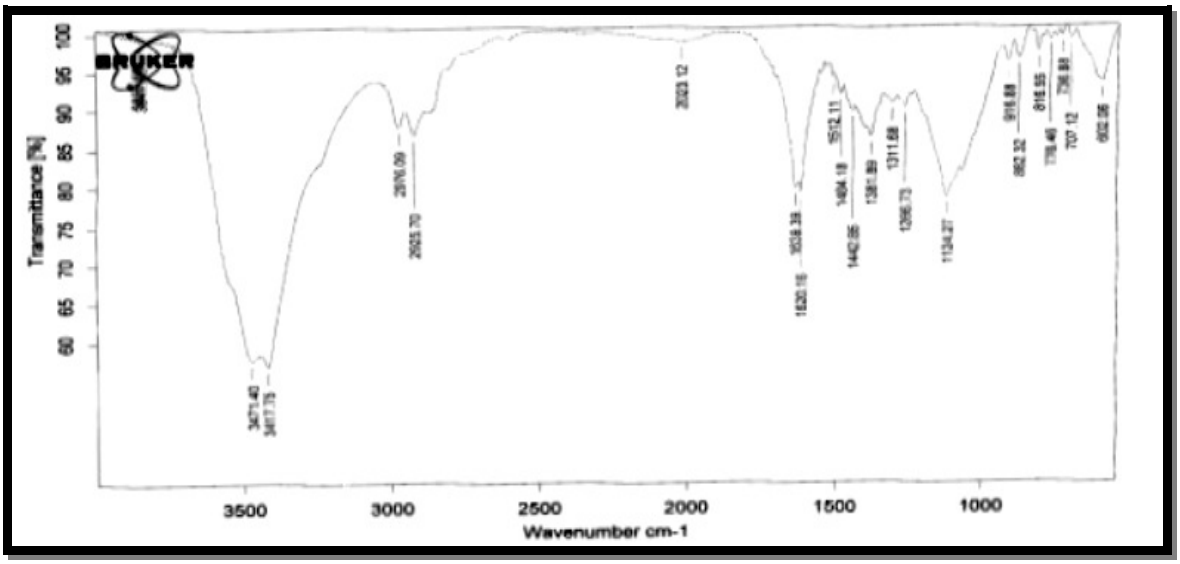


Figure 15: I.R spectrum of Drug +Ethyl cellulose

Table 16: Comparision of the characteristic I.R peaks corresponding to the functional groups in Tolterodine tartarate with physical mixture of different excipients

Correspondig functional groups	**Literature value (wave numbercm^{-1})**	**Characteristc peaks of drug alone (wave number cm^{-1})**	**Drug +HPMC (wave number cm^{-1})**	**Drug +EC (wave number cm^{-1})**
Tertiary amine group N-H stretching	3500-3100	3415.54	3416.32	3417.75
Aliphatic alkane C-H stretching	2960-2850	2944.95	2924.22	2925.70
Phenolic O-H stretching	1300-1200	1212.39	1009.43	1124.27
Aromatic C=C group stretching	1600-1450	1598.77	1619	1620.16

6.5. Evaluation of Pellets:

6.5.1. Sieve Analysis:

All the Tolterodine Tartrate formulations were tested for particle size by sieve analysis using mechanical sieve shaker. Not more than 90% of pellets pass through 18 number mesh and not less than 90% pellets are retained on 22 number mesh.

6.5.2. Percentage Moisture content:

30ml of methanol is taken in a clean, dried Karl Fischer titration flask and titrated with KF reagent until the end point to neutralize the free water. Tolterodine Tartrate pellets are powdered finely. Accurately weighed quantity of 0.5gm of sample is transferred to the titration flask and dissolved by stirring and titrate with KF reagent to the end point and percentage water content is calculated

Table 17: Percentage Moisture content

S. No	Formulation	% Moisture Content
1	Trial I	1.72
2	Trial II	1.95
3	Trial III	1.81
4	Trial IV	1.88
5	Trial V	1.92
6	Trial VI	1.89
7	Trial VII	1.87
8	Trial VIII	1.85

6.6. Evaluation of Capsules Containing Pellets:

6.6.1. Weight variation:

20 intact capsules are selected randomly and weighed and average weight is calculated. Individual weight of each capsule is determined. According to USP, none of the individual capsule weight should be less than 90% and more than 110% of the average weight.

Table 18: Weight Variation

SNo	Formulation	Average Weight (mg)
1	Trial I	333.5 ± 3.6
2	Trial II	334.2 ± 5.8
3	Trial III	333.7 ± 4.5
4	Trial IV	334.5 ± 3.5
5	Trial V	333.6 ± 3.2
6	Trial VI	333.3 ± 4.5
7	Trial VII	334.1 ± 4.6
8	Trial VIII	333.6 ± 3.7

6.6.2. Content Uniformity:

Capsules containing Tolterodine Tartrate formulations have shown the drug content uniformity in the range of 98.3%-100.5%. According to USP, 30 intact capsules are selected, of which 10 are assayed. 9 of 10 capsules should be within the potency range of 85%-115%. The potency of 10^{th}capsule should not exceed the range of 75-125%

Table 19: Content Uniformity

SNo	Formulation	%Drug Content
1	Trial I	98.5 ± 0.2
2	Trial II	99.7 ± 0.3
3	Trial III	100.1 ± 0.2
4	Trial IV	99.5 ± 0.4
5	Trial V	98.3 ± 0.3
6	Trial VI	99.7 ± 0.4
7	Trial VII	99.9 ± 0.2
8	Trial VIII	100.1± 0.3

6.6.3. Assay by HPLC

100µl, six replicate injections of standard solution and single injection of sample solution were injected. The chromatograms are recorded and the peak response was measured. The assay (in %) was calculated by using following formula.

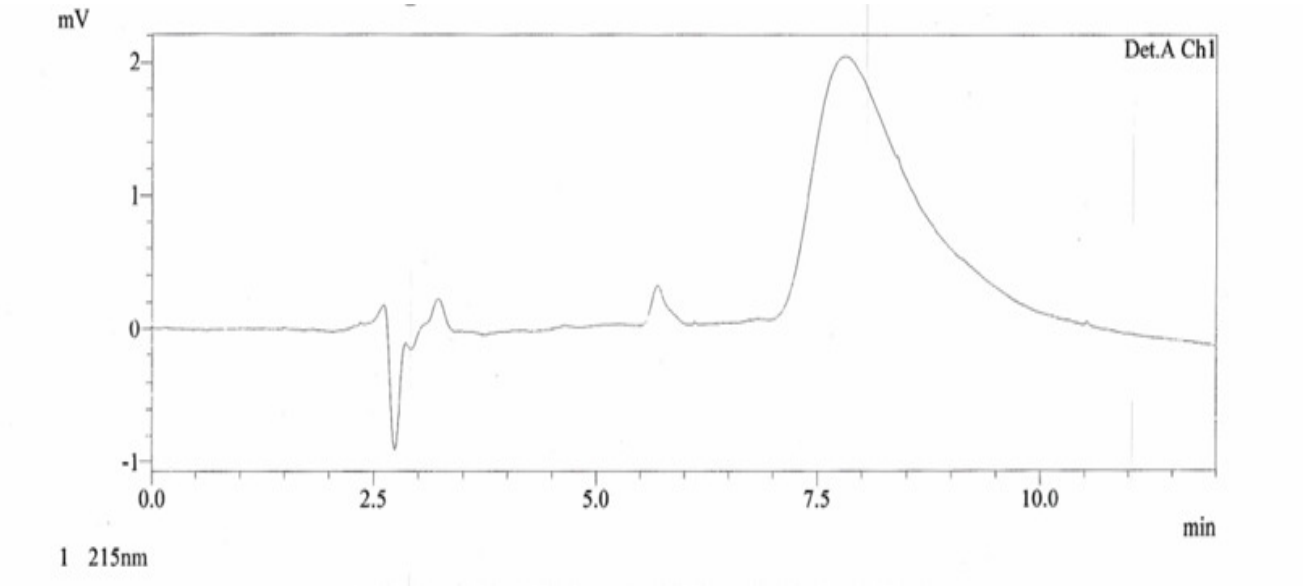
$$\%\text{Drug Content} = \frac{A_T}{A_S} \times \frac{W_S}{50} \times \frac{2}{100} \times \frac{250}{W_T} \times \frac{50}{5} \times \frac{P}{100} \times \frac{100}{\text{Label claim}} \times 100$$

Where,
A_T = Peak area of Tolterodine Tartrate in sample solution
A_S = Average peak area of Tolterodine Tartrate in standard solution
W_S = Amount of Tolterodine Tartrate taken in working standard (mg)
W_T = Amount of sample (mg)
P = Potency of Tolterodine Tartrate working standard used.

Capsules containing Tolterodine Tartrate formulations have shown the assay (in %) in the range of 92.7%-100.1%.

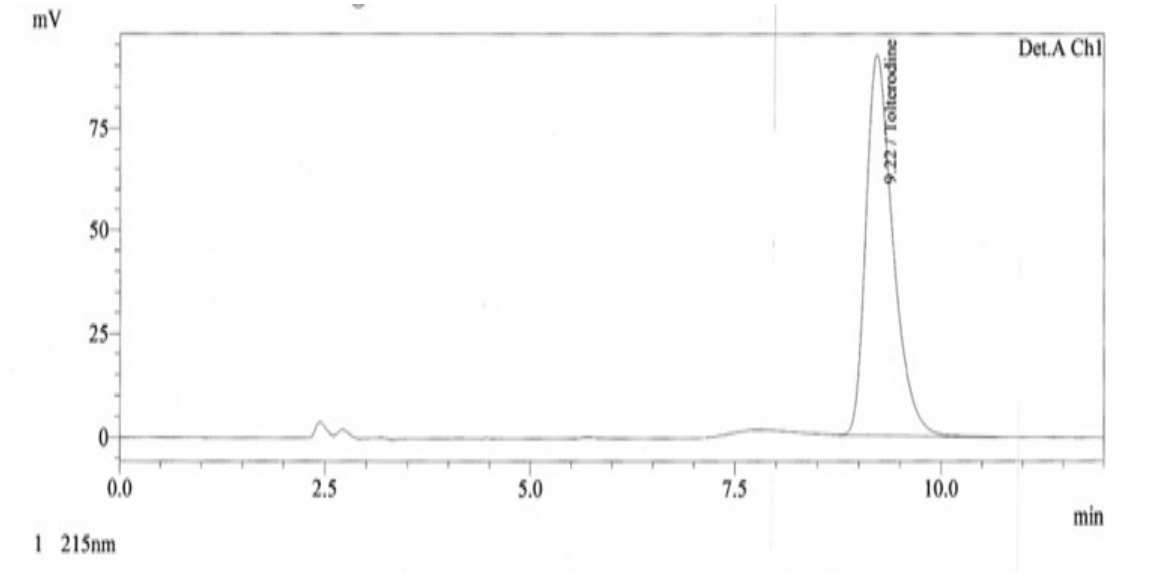
Table 20: Percentage Drug Content

S No	Formulation	%Drug Content
1	Trial I	93.5 ± 0.2
2	Trial II	92.7 ± 0.3
3	Trial III	95.1 ± 0.2
4	Trial IV	94.5 ± 0.4
5	Trial V	97.3 ± 0.3
6	Trial VI	95.7 ± 0.4
7	Trial VII	98.2 ± 0.2
8	Trial VIII	100.1± 0.3



Chromatogram

Fig.16: Assay Of Blank Solution

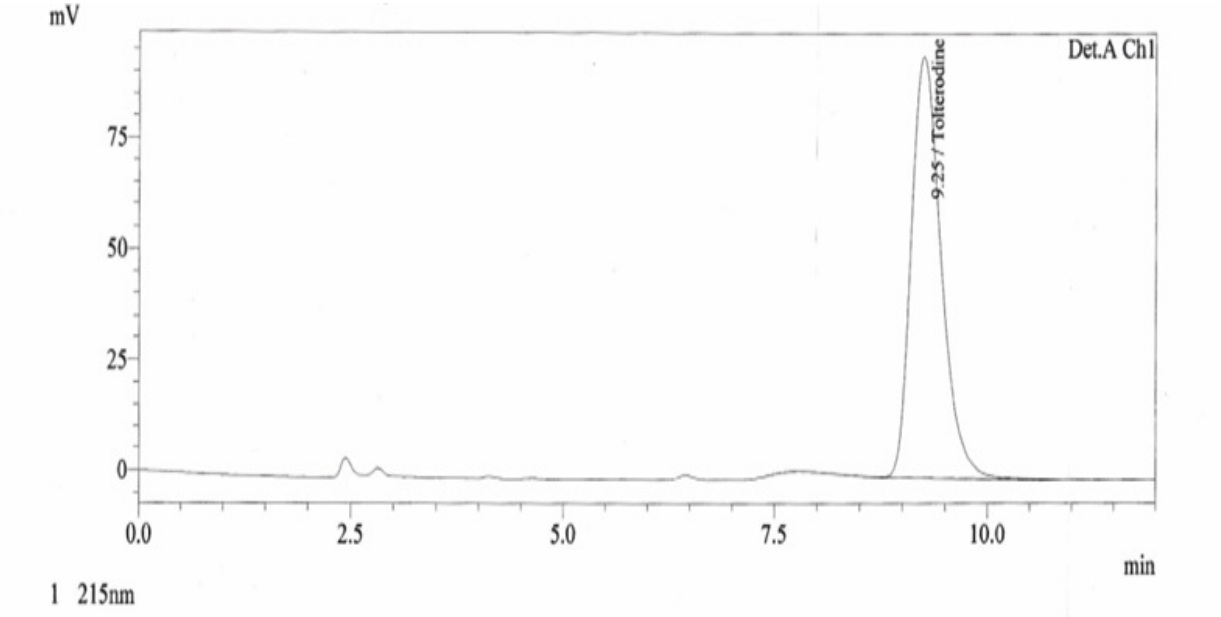


Chromatogram

Detector Ach 1 215nm

Peak #	Name	Ret. Time	Area	Area%	Theoretical plate #	Tailing factor
1	Tolterodine	9.22	2098348	100.00	3950	1.4
Total			2098348	100.00		

Fig. 17: Assay Of Standard Solution



Chromatogram

Detector Ach 1 215nm

Peak #	Name	Ret. Time	Area	Area%	Theoretical plate #	Tailing factor
1	Tolterodine	9.25	2309750	100.00	3440	1.4
Total			2309750	100.00		

Fig. 18: Assay Of Sample Solution

6.6.4. Dissolution by HPLC:

100µl of dissolution media, six replicate injections of standard solution and single injection of sample solutions were separately injected into the chromatograph. The chromatograms were recorded and peak responses were measured.

% labeled amount of Tolterodine Tartrate dissolved

$$\frac{A_T}{A_S} \times \frac{W_S}{50} \times \frac{1}{100} \times \frac{900}{W_T} \times P \times 100$$

$$\frac{A_T}{A_S} \times \frac{W_S}{50} \times \frac{1}{100} \times \frac{900}{W_T} \times P \times 100 = \text{\% Label Claim}$$

Where,

A_T = Absorbance of Tolterodine Tartrate sample solution

A_S = Absorbance of Tolterodine Tartrate standard solution

W_S = Weight of Tolterodine Tartrate in working standard(mg)

W_T = Weight of Tolterodine Tartrate pellets taken (mg)

P = Potency of Tolterodine Tartrate working standard used

Table 21: Innovator Drug Release Profile

SNo	Time(hrs)	%Drug release
	0	0
1	1	23.30
2	2	46.7
3	4	71.5
4	8	93.5

Table 22: Comparative Dissolution Data

S. No	Time (hrs)	%Drug Release								
		Innovator	Trial I	Trial II	Trial III	Trial IV	Trial V	Trial VI	Trial VII	Trial VIII
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	1	**23.30**	10.3	11.3	12.7	17.5	18.2	19.7	29.5	25.50
2	2	**46.7**	21.8	22.4	23.8	25.1	30.4	33.8	42.1	49.10
3	4	**71.5**	38.1	38.9	41.3	59.5	60.8	64.3	68.5	74.50
4	8	**93.5**	56.7	59.7	68.3	78.4	81.6	84.3	89.4	95.60

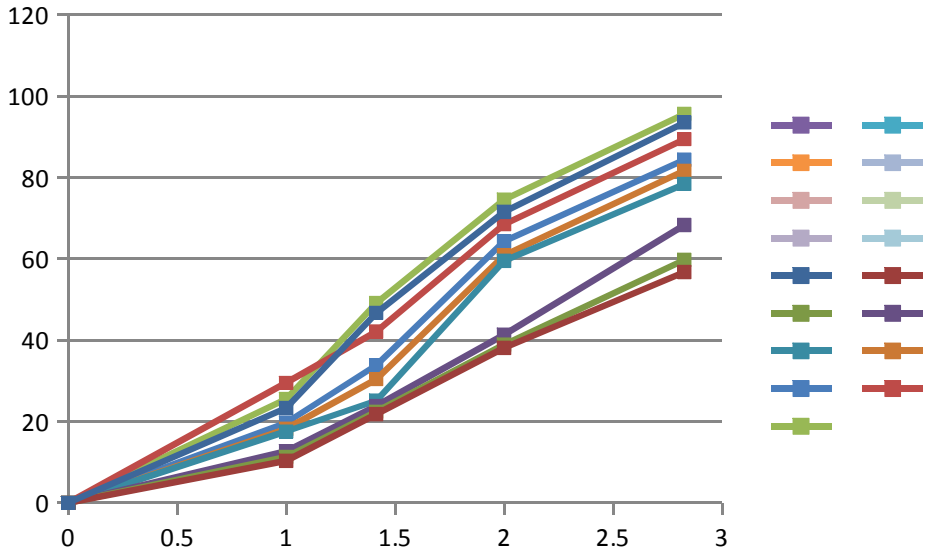


Fig: 19. Comparative *in vitro* drug release profile of Trials I-VII1

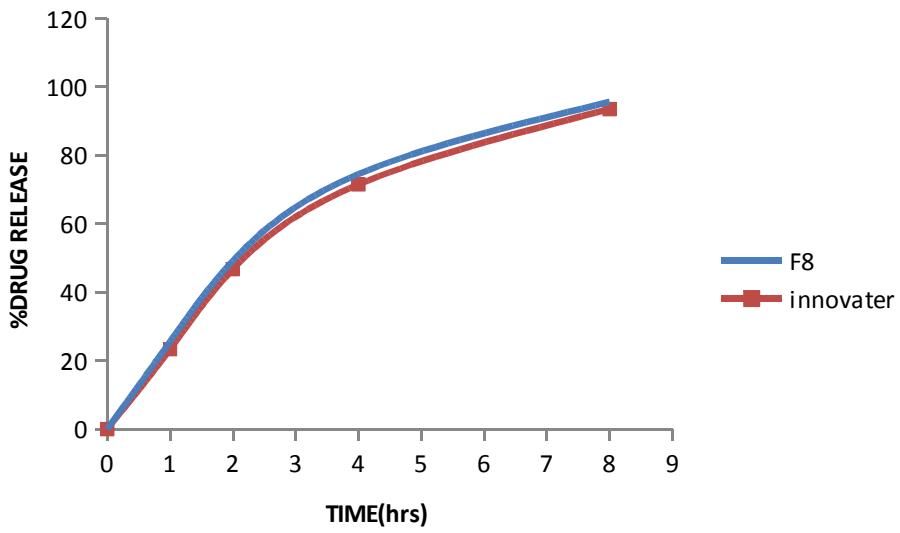


Figure 20.Comparative *in vitro* drug release profile of Trial VIII (optimized trial) with Innovator

Eight formulations of sustained release pellets were prepared by incorporating Ethyl cellulose and PVPK-30 as a pore former. From the initial 3 trials with the varying concentration of Ethyl cellulose the dissolution results suggested that when the concentration was high the drug release was retarded from initial to the end point and at low concentration the drug release was higher than the reference product at the initial hours and incomplete release at the end of the dissolution. By observing the incomplete release from the coated pellets even at low concentration of Ethyl cellulose a barrier coating polymer is incorporated from trial 4 and varying the concentration of Ethyl cellulose was studied. From all the above studies it is concluded that the batch with 4.3% of HPMC as barrier coat and 3.2% Ethyl Cellulose with 1.6% of PVPK-30 found to be the best of all the trials matching the innovator product. For all the batches the prepared pellets were filled in to Size 3 capsules and analyzed.

6.6.5.DRUG RELEASE KINETICS:

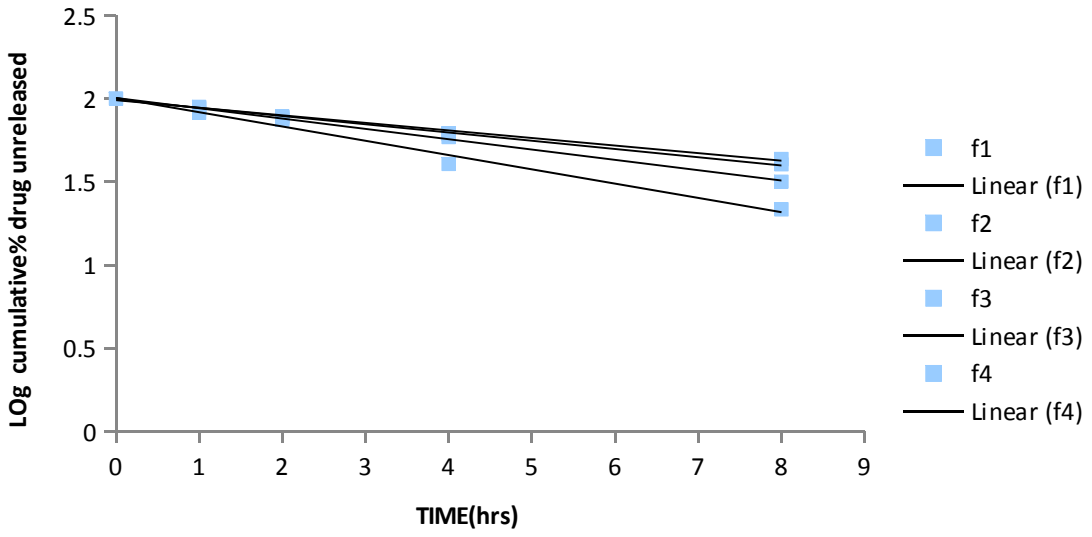


Figure 21: First order graph kinetics of Trials I-IV.

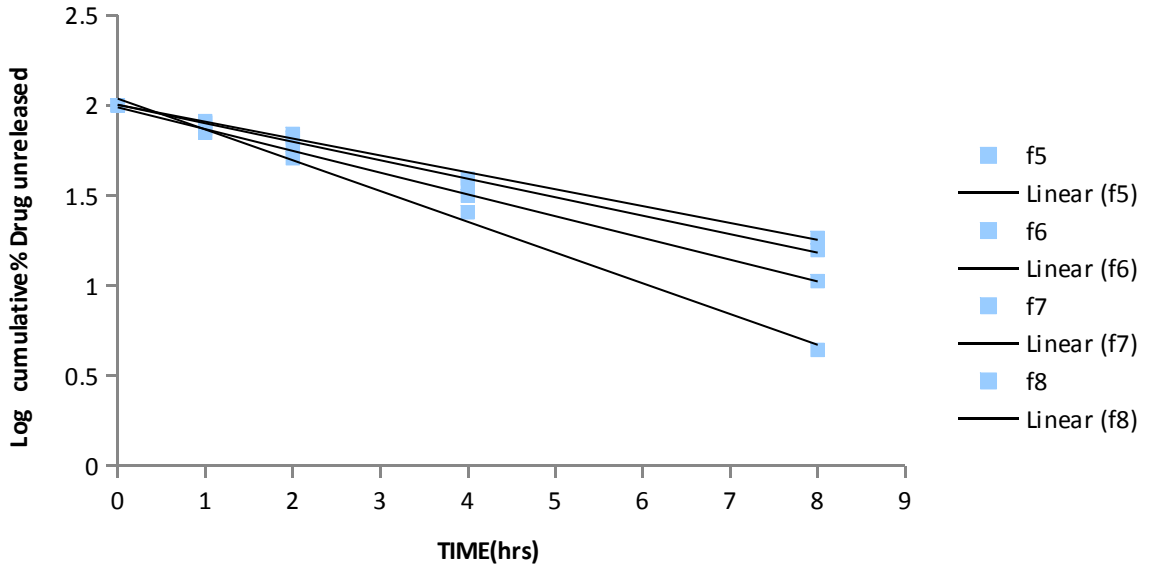


Figure 22: First order graph kinetics of Trials V-VIII.

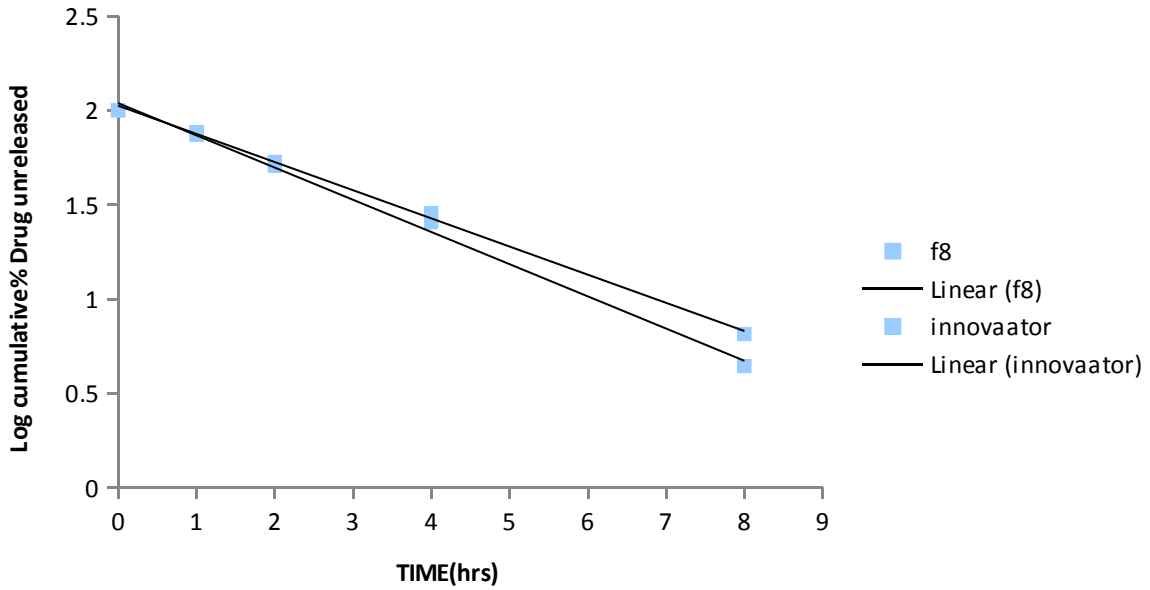


Figure 23 : First order graph of innovator & optimized trail (f8)

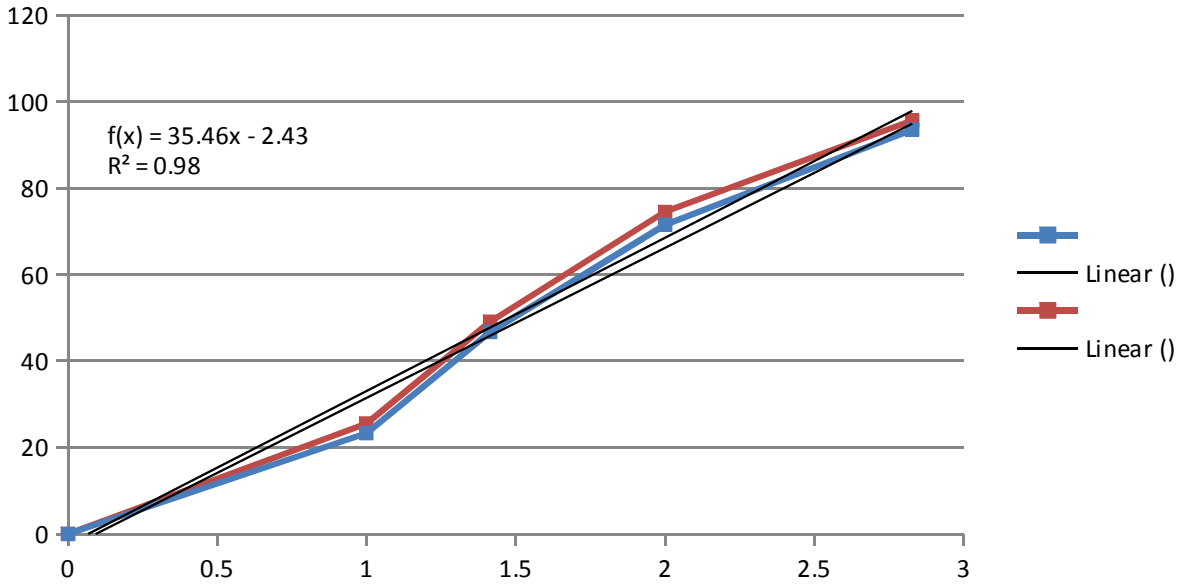


Figure 24 : Higuchi plot of innovator product & optimized trial (f8)

The kinetic analysis of the drug release data reveal that the pattern of drug delivery follows first order and matrix diffusion as shown by the straight lines (FIG 21-24).

6.6.6. F_1& F_2 Values for formulations:

A dissolution profile characterizes the product more precisely than a single point dissolution test. It helps to assure similarity in product performance and signals bioequivalence. The factor f1 is proportional to the average indifference between two profiles, where as factor f2 inversely proportional to the average squared indifference between two profiles

$f1 = \Sigma D\ (1/\ \Sigma t)\ 100$

$f2 = 50 \times \ln\{1/1+\Sigma\ (Rt-Tt)^2\}$

The mean dissolution values of the two profiles (test and innovator) are taken which were made under same test conditions and same time points. The time points were taken as 1, 4, 7 hours. The above mathematical approach is made to compare the dissolution profiles of Tolterodine Tartrate pellets using two factors f1 and f2. The Similarity and Dissimilarity values for the optimized Trial VIII were found to be 5.49and 79.36 respectively.

Table 23: Similarity and Dissimilarity Values for formulations

Value	Trials							
	Trial I	**Trial II**	**Trial III**	**Trial IV**	**Trial V**	**Trial VI**	**Trial VII**	**Trial VIII**
F_1	17.17	9.39	9.39	5.76	22.77	22.87	11.45	5.49
F_2	45.19	58.09	57.98	68.21	40.11	40.54	54.91	79.36

6.6.7. Stability Results:

Table 24: Stability Results for selected formulation

SNo	Test	Storage Condition 40ºC ± 2ºC /75%RH ± 5%RH		Storage Condition 25ºc ± 2ºC /60%RH ± 5% RH	
		Initial	90 days	Initial	90 days
1	Physical Appearance	White	White	White	White
2	% Moisture Content	1.25	1.26	1.25	1.25
3	% Drug Content	100.1	99.9	100.1	100
4	% Drug Release	93	92.9	93	92.9

It was concluded that stability studies of the optimized Trial VIII was carried out using the samples at different temperatures 40^0C ± 2^0C, 75% ± 5%RH and 25^0C ± 2^0C, 60% ± 5%RH for a period of three months, the capsules are observed and there is no significant change in the release characteristics and physicochemical properties of the capsules.

CHAPTER-7

SUMMARY AND CONCLUSION

7. SUMMARY AND CONCLUSION

Tolterodine is an antimuscarinic drug that is used to treat urinary incontinence. It is a tertiary amine with relatively low lipophilicity. Tolterodine has a pronounced effect on bladder function. The main effects of Tolterodine are an increase in residual urine, reflecting an incomplete emptying of the bladder, and a decrease in detrusor pressure, consistent with an antimuscarinic action on the lower urinary tract.

The main aim and objective was to develop Sustained release capsules of Tolterodine Tartrate in order to meet the required bioavailability and to study the in-vitro release pattern of the test formulation against the Innovator product.

In the current study Tolterodine Sustained release pellets were prepared by Layering of the drug on core pellets by fluid bed processor (Wurster) and coating of the drug layered pellets with the sustained release polymers with the same process of Fluid bed processor (Wurster). For the layering of the drug on core pellets the drug solution was prepared by using HPMC as a binder with the suspension layering technique. HPMC at 6% concentration was used constantly and at 6% concentration the Drug layered pellets is found to be satisfactory without any doublets or triplets. Further the pellets assay results suggested that there is no loss of drug. Hence throughout the process the concentration of HPMC for drug layering maintained constantly at 6% level.

Eight formulations of sustained release pellets were prepared by incorporating Ethyl cellulose and PVPK-30 as a pore former. From the initial 3 trials with the varying concentration of Ethyl cellulose the dissolution results suggested that when the concentration was high the drug release was retarded from initial to the end point and at low concentration the drug release was higher than the reference product at the initial hours and incomplete release at the end of the dissolution. By observing the incomplete release from the coated pellets even at low concentration of Ethyl cellulose a barrier coating polymer is incorporated from trial 4 and varying the concentration of Ethyl cellulose was studied. From all the above studies it is concluded that the batch with 4.3% of HPMC as barrier coat and 3.2% Ethyl Cellulose with 1.6% of PVPK-30 found to be the best of all the trials matching the innovator product. For all the batches the prepared pellets were filled in to Size 3 capsules and analyzed.

The kinetic analysis of the drug release data reveal that the pattern of drug delivery follows first order and matrix diffusion as shown by the straight lines.

The identified formulation f8 which was matching to the reference product on the basis of f1, f2 values was manufactured again with the same process parameters to confirm the reproducibility. The result of the reproducibility batch is found to be superimposable to the final identified formulation.

Stability study was carried out for 3 months at 25°C±2°C; 60%±5% RH: and 40°C±2°C; 75% ±5% RH, according to ICH guidelines for the final formulation and the results are found to be stable.

The optimized formula shall be utilized for the formulation development and other studies like bio-equivalence study, for successful launching of the product.

CHAPTER-8

BIBLIOGRAPHY

8. BIBLIOGRAPHY

1. **Agis Kydonieus,** Treatise On Controlled Drug Delivery, Fundamentals. Optimization. Applications. Marcel Dekker, Inc, Page.No.330-331.(2001)
2. **Lee TWY, Robinson JR.,** Remington: The Science and Practice of Pharmacy, 20th edition, Page.No. 1069-70, (2000).
3. **Howard C. Ansel, Loyd V. Allen, Nicholas G. Popovich.,** Ansel's Pharmaceutical Dosage forms and Drug Delivery Systems, 8th edition, Page.No. 268, (2009).
4. **Chien W. Y,** Novel Drug Delivery Systems. Marcel Dekker, Inc., New York, vol.50, Page.No. 156-165, (1992).
5. **Robinson JR, Lee VH,** Controlled Drug Delivery: Fundamentals & Application, Vol.36, Marcel Dekker, New York (NY). 2nd edition, (1987).
6**. Aulton M.E,** International Student Edition, Pharmaceutics-The Science of Dosage form design, Page.No. 290, Churchill Livingston, (2001).
7. **Leon Lachman, Joseph L, Kanig,** The theory and practice of industrial pharmacy, 3rd edition, Page.No. 331-2, 364-8, (1986).
8. **William Andrew**, 3rd edition. Pharmaceutical Manufacturing Encyclopedia, Volume 1.
9. **Jain NK.,** Advances in Controlled and Novel Drug Delivery, 268-269. CBS Publications, New Delhi, (2000).
10**. Graham cole, John Hogan and Michael aulton,** Pharmaceutical Coating Technology, by Informa health care, Page.No.205-209, 410-411, (2008).
11. **Ghebre-Sellassie, I.** Pellets: A General Overview. In: Ghebre-Sellassie, I. (edition.) Pharmaceutical Pelletization Technology. Marcel Dekker, New York, Page.No 1-13, (1989a)

12. **James Swarbrick,** Encyclopedia of Pharmaceutical Technology, 3rdedition, Page.No. 1256-1261, Marcel and Dekker, New York, (2002).
13. **Leon Lachman, Herbert A. Lieberman, Joseph K. Kanig**: The theory and practice of industrial pharmacy; 3rd edition, Page.No. 348-352, 426, (2009).
14. **S.P. Vyas and Roop K. Khar,** Controlled Drug Delivery. Concepts and Advances, Page.No. 167-168, 173-174, (2005).
15. **Sarfaraz K, Niazi,** Handbook of Pharmaceutical Manufacturing Formulations Compressed Solid Products, volume one, second edition, Page.No. 328.
16. **A.Lieberman, Leon lachman, and Joseph B.schwartz,** Pharmaceutical Dosage Forms: Tablets Volume 3, IInd edition, Marcel Dekker,Inc, Page.No.125-127, (2005).
17. **Raymond., C.R., Paul, J.S., Sian**. C.O., 2006. 'Handbook of pharmaceutical excipients' Fifth Edition: 278-283.
18. **Jamesc. Bolyan,jockcooper** Hand book of pharmaceutical excipients 5th edition.
19. **Kammili Lavanya**, Pelletization Technology: A Quick Review, International Journal of Pharmaceutical Sciences and Research, Vol. 2, Issue 6, (2011).
20. **Rang and Dales** Pharmacology. H.P.Rang, M.M.Dale, 6th edition, Page.No.385-388.
21. **JoleG. Hardman, LeeE. Limbird,** Goodman & Gillman's, The Pharmacological Basis of Therapeutics, 10th edition, Page.No. 1005-1009.
22. **Anette, P., Klaus, K., Bernhard, C. L**., 2010. 'Preparation of sustained release matrix pellets by melt agglomeration in the fluidized bed: influence of formulation variables and modelling of agglomerate growth.' Eur.J.Pharm.Biopharm., 74 : 503–512.
23. **Anroop, B**., **Hiral,V., Ashok,K**., 2010. 'Controlled release matrix uncoatedtablets of enalapril maleate using hpmc alone.' J.Basic.Clin. Pharm., 1(2): 71-75.
24. **Aulton, M**., International student Edition, 2001. Pharmaceutics-The Science of Dosage form design, 129-191. Churchill Livingston.
25. **Barde, L**., **Bhutada, D., Mathur, V., Shivhare**, U.,2011. 'Synthesis of hpmc and its application as coating material for sustained release diltiazemhcl tablet.' Int.J.Uni.Pharm.L.Sci., 1(2): 135-148.
26. **Olsen, K., Ghebre-Sellassie**, I., 1sted, 1989.Pharmaceutical Pelletization Technology, 39-69. Marcel and Dekker, New York.

27. **Shah P., Mashru R., Rane Y**., 2007. 'Stability testing of pharmaceuticals'. J. pharm. research., 6: 1-9.
28. Drugbank website [online]. Available from: http://**www.drugbank.ca/**drugs/
29.**Fu, J., Wang, X., Xu, L., Meng, J., Weng, Y., Li, G., He, H., Tang, X**., 2011. 'Preparation and in vitro–in vivo evaluation of double layer coated and matrixsustained release pellet formulations of diclofenac potassium.' Int. J. Pharm., 406:84–90.
30. **Pandit vinay, Khanum aisha., Banu Vasiha.,**2008. 'Preparation and evaluation of Tolterodine Tartrate TransDermal Films for the treatment of over active bladder.' V-1 : 516-521
31. **Lighang Zhoa., Y Li., L fang, Z He.,** 2008. 'Tolterodine – Tolterodine Tartrate TransDermal Films.'., 327 : 195–207.
32. **Fengying S., Sui, Cheng.; Teng,**, 2010.,trove.nla.gov.au/work/40217498.
33. **Kreder k., Eur Urol.** 2002. 'Tolerability and efficacy of extended release tolterodine in the treatment of overactive bladder" Detrol@LA 41: 588–595.
34. **Brizzi Maria P; Berruti Alfredo, Milanesi Enrica** 2010. 'Development And Investigated release mechanism of theo phylline pellets coated with aqueous Ethyl Cellulose.'
35. **Kang Ji Hye, Gonghua.** 2012. 'Prediction of drug release from ethylcellulose coated pellets.' J. Contr.Release., 135: 71–79.
36. **Namrata gautam** 2012. 'Formulation of multiparticulate modified release pellets of Tolterodine Tartrate.' Volume-2., issue-2.,
37. **Nanda, RK.,Gaikwad, J., Prakash, A**., 2009. 'Simultaneous spectrophotometric estimation of tolterodine in pharmaceutical dosage form.' Research J. Pharm. and Tech., 2 (2): 312-314.

.